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CHEMOTHERAPY OF RODENT MALARIA
EVALUATION OF DRUG ACTION AGAINST NORMAL AND
RESISTANT STRAINS, INCLUDING EXO-ERYTHROCYTIC STAGES,

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WALLACE/PETERS MD, DSc

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Department of Parasitology
Liverpool School of Tropical Medicine
Pembroke Place,
Liverpool L3 5QA, UK

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<p>Data are provided on the blood schizontocidal action of 8 WRAIR compounds and the tissue schizontocidal activity of a total of 110 WRAIR 8-aminoquinolines plus 29 other compounds. Emphasis is laid on the comparison of a new series of 5-substituted 8-aminoquinolines and comparison has been made between data obtained in our rodent models and reports on work in simian models from other investigators. A good parallel was found with tissue schizontocidal activity.</p> <p>The administration of mixtures of mefloquine with pyrimethamine, sulphaphenazole or</p>		

✓ Primaquine has been shown to enhance the development of resistance by P. berghei to the individual components.

Studies have continued on the modes of action of mefloquine, chloroquine and quinine. Mefloquine has been shown to have relatively little effect on the uptake of adenosine. The synergistic action of chloroquine and erythromycin against chloroquine-resistant parasites has been further investigated. The mechanism of this synergism is still obscure. Other work has involved the study of electron transport and cathepsins of rodent malaria parasites.

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WALLACE PETERS, MD, DSc

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Liverpool L3 5QA, UK

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1. INTRODUCTION

In this Report we review work carried out between the termination of our last contract on 31 October 1975 through 31 December, 1976. Details of this work have been provided in Quarterly Reports Numbers 1 through 3.

The main emphasis of this year's studies has been the evaluation in depth of the causal prophylactic potential of new WR compounds and a comparison of the data obtained in our rodent malaria screen with that of Dr. Leon Schmidt's rhesus-P. cynomolgi system¹.

Another major item of our programme has been the follow-up of studies to evaluate the effect of polytherapy in reducing the rate at which P. berghei develops resistance to mefloquine. Details of this study are now ready for publication and summaries are included in the following pages.

Further studies have been made on the effect of several compounds against the sporogonic stages of rodent malaria, and on the fundamental biochemical processes of the blood stages, especially glycolysis.

2. CYCLICAL PASSAGE OF RODENT MALARIA STRAINS

We have continued to rely on the P. yoelii nigeriensis-Anopheles stephensi combination for the supply of infected mosquitoes for chemotherapy investigations. A temporary falloff in oocyst development was finally traced down to fluctuations in the temperature of the insectary due to a defective thermostat. Replacement of this has brought our cyclical transmission back to normal levels.

3. PRODUCTION OF DRUG-RESISTANT LINES

3.1 NS-type lines of P. berghei

After several years of research and soul-seeking we have been able to reach the conclusion that several strains of P. berghei from highland areas of the Katanga region of Zaire are in fact a mixture of two species. The importance of this will be appreciated when it is pointed out that one of the mixture, P. berghei sensu stricto, is chloroquine sensitive, and the other which we call "P. yoelii ssp." is innately chloroquine-resistant. These conclusions must influence our interpretation of all work carried out up to now on isolates of rodent malaria from this part of Africa. The following is the summary of a paper now submitted for publication on this topic².

¹Under chloroquine selection pressure a number of chloroquine-resistant lines of rodent malaria have been selected from "strains" of "P. berghei" originating in the Katanga highlands. They are called the "NS lines". No resistant parasite was obtained from a clone under drug pressure, nor from two other highland P. berghei and a strain of P. v. vinckei.

The isoenzyme typing of these parasites indicates that the drug-resistant NS parasites are allied to P. yoelii rather than P. berghei, but that they can be distinguished from all but the subspecies P. y. nigeriensis, sharing with this GPI 2, 6PGD 4, LDH11 and GDH 2. The resistant organism is therefore labelled P. yoelii ssp.

The buoyant density of all P. berghei and P. yoelii subspecies examined is identical (1.683 g/ml). DNA-DNA hybridisation studies have shown that P. yoelii ssp. differs significantly not only from P. berghei, but also from P. y. yoelii and P. y. nigeriensis in terms of the base sequence homologies of these parasites.

Cross-immunity experiments indicate that P. yoelii ssp. differs not only from P. berghei, but also from P. y. nigeriensis in the absence of reciprocal cross-protection, although P. berghei itself (as well as the mixtures containing P. yoelii ssp.) provide a broad and relatively non-specific protection against the other parasites.

Evidence is presented to refute the suggestion that the "NS lines" have become accidentally mixed with P. berghei in the laboratory. On the contrary, the evidence indicates that the NS lines are not P. y. nigeriensis but a new subspecies in the P. yoelii complex. How such mixtures of P. berghei and P. yoelii ssp. have survived through many years and countless syringe passages in the laboratory is unknown, but this is not an isolated instance in the history of the rodent malaras. The existence of P. yoelii ssp. may account for a number of previously unaccountable observations in the laboratory such as some of the apparent "variability" of P. berghei "strains" under a variety of experimental conditions.

The importance of these findings is discussed in relation to the zoogeography of the rodent malaras.'

3.2 Polytherapy in the prevention of drug-resistance

We have already reported the relative ease with which resistance can be developed to mefloquine, and preliminary data on our attempts to decrease the rate at which this resistance develops through the use of drug mixtures. Using a relapse technique resistance of P. berghei N strain to mefloquine can be developed slowly (Fig. 1), but the progress is more rapid in the chloroquine-resistant NS lines. Mefloquine resistance in all these lines is very unstable in the absence of drug selection pressure (Fig. 2).

Resistance develops also when the N strain is submitted to slowly increasing mefloquine dosage in consecutive passages (Fig. 3), the resulting parasites having a similar morphology at light microscope level to chloroquine-resistant P. berghei RC line parasites. Like the latter they occupy polychromatophilic red blood cells almost exclusively.

When the parasites are exposed to mixtures of mefloquine with pyrimethamine, sulphaphenazole or primaquine, resistance to each component of the mixtures develops more slowly than to the individual components used alone (Figs. 4 to 6).

It is strongly recommended that mefloquine should only be deployed for the prevention or treatment of malaria in man caused by chloroquine-resistant *P. falciparum*. For large-scale use mefloquine should not be employed until a second antimalarial has been identified that will minimise the risk of parasites becoming resistant to this potentially valuable new compound.

A full report on this work has been submitted for publication³.

4. CHEMOTHERAPY STUDIES

4.1 Blood schizontocides

4.1.1 New compounds

The evaluation of new compounds for blood schizontocidal activity has been restricted to some 8 compounds on which data were provided in our 3rd Quarterly Report. Three compounds showed good activity against the drug-sensitive N strain of *P. berghei*, namely WR 219,930, 194,965, and 225,449, the last two being somewhat more effective than the first. No studies were made in drug-resistant lines with these compounds.

4.1.2 Drug combinations

The main purpose of our drug combination work this year was to determine whether those combinations with mefloquine that we have shown to reduce the rate of resistance development possessed additive or even potentiating properties. The details were given in our 3rd Quarterly Report and are to be published⁴.

The data summarised in Fig. 7 indicate that there is certainly no potentiation between mefloquine and primaquine, or mefloquine and sulphaphenazole. There is a slight indication of potentiation between mefloquine and pyrimethamine but possibly only of the order that could be anticipated if the two compounds influence each other's pharmacokinetics in the host.

4.2 Causal prophylaxis- the value of the rodent screen

The greater part of our work has been devoted to examining the causal prophylactic potential of new WR compounds in our rodent malaria model. We have examined altogether some 110 WRAIR 8-aminoquinolines plus 5 from other sources, 6 naphthyridines and 18 miscellaneous compounds that are covered in the present report. Other miscellaneous compounds have been dealt with in previous Quarterly and Final Reports over the years.

We have presented these data in tabular form (Tables 1 through 14) and in these we include our own interpretation of Minimum Fully Curative Doses (MCFD) presented in Schmidt's Final Report of 1976. The figures we give for the MCFD values take into account dose levels at which cure was obtained only in some animals but not in all treated at any particular level, and the values are converted to $\mu\text{M base/kg}$. In our rodent model animals were routinely treated on a single occasion, by the sc route and it is only recently that we have started to use also the oral route. For this reason there are still many blanks in Tables 1 through 14 that we will be filling in on the basis of ongoing studies. This makes a direct comparison of the 145 compounds that both we and Schmidt have examined difficult at the present time. As we have pointed out previously it is, in a way, surprising that there should be any correlation between our data. Schmidt uses a different parasite, different host, different route of administration and different dosage schedule from ourselves. Nevertheless on the basis of the primaquine indices as we have calculated them so far we find a remarkably good correlation between our data in the majority of the 8-aminoquinolines series.

There is however one important area in which we differ considerably and that is the area represented by poorly soluble and (probably) poorly orally absorbable compounds such as menoctone (WR 49,808) and WR 226,626. This type of compound we believe to be extremely interesting since those members that we have examined have proved to possess not only tissue schizontocidal properties but also good activity against both drug-sensitive and drug-resistant blood stages of P. berghei. In this sense we believe that the rodent malaria screen offers advantages over the rhesus-P. cynomolgi screen. While appreciating the great value of the simian model we do feel that many important leads may be missed if total reliance is placed on this and that the rodent screen has a most valuable contribution to make as we have indicated elsewhere⁵.

Data on compounds still receiving preliminary screening are presented in Table 15 through 38, while completed sheets not yet forwarded to WRAIR form Tables 39 through 53.

4.3 Sustained release of drugs

The work on the sustained release of antimalarials from polydimethylsiloxane capsules reported in the 3rd Quarterly Report 1976 (2.4) has been continued and expanded. To date pyrimethamine filled capsules having a wall thickness of 0.63 mm and an internal surface area of 105 sq. mm. have afforded complete protection to mice against P. berghei (N strain) challenge for a period of 102 days. Capsules with an internal surface area of approximately 25 sq. mm. gave mice a survival time of between 55 and 65 days though all mice had patent parasitaemias from approximately day+38 onwards. Very similar results were obtained with capsules having an internal surface area of approximately 50 sq. mm.

No antimalarial effect was observed with encapsulated cycloguanil, WR 99209 and WR 99210. Promising preliminary results have been obtained with another cycloguanil analogue and menoctone and these compounds are being studied in greater detail.

Current experiments are designed to utilise drug capsules prepared by mixing drug and pre-vulcanised silastic as described by Fu et al.⁶ and drug incorporated into biodegradable polymers.

4.4 Mode of drug action

4.4.1 Chloroquine and mefloquine

The method by which chloroquine kills the malaria parasite is still not known. Its short-term effect in causing the clumping of haemozoin has been investigated in considerable depth, but haemozoin clumping itself does not kill the parasite. We are therefore investigating the time at which the parasite dies after treatment with chloroquine and the way in which the action of mefloquine differs from that of chloroquine.

The clumping of malaria pigment by chloroquine (10^{-6} M) is complete within 80 minutes but there is no effect within this time on growth of the parasite, as measured by the incorporation of radio-active adenosine. Six hours after treatment of P. berghei-infected mice with chloroquine (60 mg/kg) incorporation of adenosine was reduced by about 25%, but after 12 hours the synthesis of nucleic acids had fallen sharply. These results suggest that P. berghei dies only after about 12 hours exposure to chloroquine and closely parallel those obtained by Davies and Howells (unpublished) in experiments on the viability of the parasite after varying times of exposure in vivo to chloroquine. Radioactive chloroquine taken up by P. berghei parasitized cells maintains its maximum intracellular concentration for at least three hours in vitro. It seems that the clumping of haemozoin is unrelated to the death of the parasite.

The effect of mefloquine on the erythrocytic stages of P. berghei has been reexamined at the light and electron microscope levels. The most obvious effects of the compound were observed in the haemozoin vesicles of the parasite, with the ultrastructural changes being broadly similar to those described in P. berghei treated with WR 122455 and quinine⁷. Within 3 hours of exposure to a single subcutaneous dose of 60 mgm/kg primary pigment clumps are formed, but not autophagosomes. With longer periods of exposure to the compound pigment grains became increasingly finer and electron translucent, with only poorly defined haemozoin grains being found in trophozoites 24 hours after treatment. These observations amplify the very slow plasmodicidal action of this compound and suggest that the drug is not solubilizing haemozoin, as was suggested for WR 122455 and quinine by Davies et al.⁷ but interferes with the catabolism of haemoglobin and/or the formation of haemozoin. Mefloquine (10^{-5} M) only slightly reduced the incorporation of adenosine by parasitized cells in one hour. A detailed study is proceeding.

4.4.2 Chloroquine and erythromycin

The synergistic action of erythromycin and chloroquine on chloroquine-resistant parasites does not appear to be due to an increased uptake of chloroquine in the presence of the antibiotic. In vitro, slightly more chloroquine was taken up by RC strain P. berghei in the presence of erythromycin but treatment of infected mice with erythromycin before measurement of chloroquine uptake in vitro, dramatically reduced the uptake of chloroquine.

No obvious effects on the ultrastructure of P. berghei (N strain) were observed following treatment with erythromycin. Studies are in progress on the effects of chloroquine and erythromycin, alone and in combination, on the RC strain P. berghei.

4.4.3 Pyrimethamine

The effects of pyrimethamine on the erythrocytic stages of P. berghei have been examined at the electron microscope level. These effects were described in the 3rd Quarterly Report of 1976.

5. PHYSIOLOGY AND BIOCHEMISTRY

5.1 Electron transport of intra-erythrocytic P. berghei

P. berghei appears to depend for energy production on a form of electron transport which differs from that of the host⁸. It therefore provides a potential target for chemotherapeutic attack. Conventional inhibitors of electron transport and uncouplers not only inhibit chloroquine-induced pigment clumping⁸ but also reduce the incorporation of adenosine into the parasites' nucleic acids (data given in the 3rd Quarterly Report 1976). The donor of electrons to the chain is not known.

Preliminary results have shown that treatment of the parasitized erythrocytes with menadione (10^{-4} M) or n-heptyl-4-hydroxyquinoline-N-oxide (10^{-5} M) reduced only slightly the utilization of glucose and the production of lactate by parasitized cells in vitro. This suggests that glucose metabolism may not be tightly linked to electron transport.

5.2 Cathepsins of parasitized erythrocytes

Our failure to isolate from P. berghei-parasitized cells a cathepsin D which was indisputably of parasite origin, and the presence of parasitized cells of a cathepsin D indistinguishable from that of mouse reticulocytes, prompted us to investigate the relationship between the number of parasites and the cathepsin activity of parasitized mouse red cells. Although results were somewhat variable (Table 54), there was little indication of an increase in catheptic activity as the parasitaemia rose. Instead, the apparent activity per parasitized cell fell, although the total activity for all cells remained approximately constant. This suggests that in the conditions used, little of the measured catheptic activity was due to the parasites. It is therefore probable that the parasites do not contain cathepsin D, and that other cathepsins must be present.

5.3 The effects of PABA on sporogonic development in *P. berghei*

As outlined in the 3rd Quarterly Report of 1976 (2.3.4) these studies were initiated to attempt to obtain results more statistically significant than those obtained by Ramkaran⁹. Initially, difficulties were encountered in the mosquito colony during our attempts to repeat this work. Abnormally high mortality rates and low infection rates in the mosquitoes were caused by excessive fluctuations of temperature and humidity in the insectaries. Examination of samples of the mosquito populations at the electron microscope level has not revealed the presence of concomitant, viral or microbial infections which might contribute to the vagaries in the malarial infections.

In recent experiments acceptable infection rates have been obtained in the mosquitoes but variations in the oocyst numbers within experimental batches are so great as to preclude the obtention of statistically significant results.

6. CONCLUSIONS AND RECOMMENDATIONS

The additional information gathered from our rodent causal prophylaxis studies has confirmed our belief that this is a valid model for tissue schizontocidal action. Taking into account the differences between our technique and that of Dr. L. H. Schmidt, there is a remarkably good parallel in our joint findings. The use of parenteral route in our rodent model will, we believe, permit us to detect activity in certain chemical groups (e.g. menoctone) the activity of which would be missed in the simian model.

During the coming year we will extend these observations and consolidate our data using both oral and parenteral routes of drug administration.

Extension of our long-term studies on drug combinations has provided useful leads for the possible protection of such promising new compounds as mefloquine. This work will be continued.

The mode of action of the antimalarials is still being investigated and fundamental gaps in our knowledge of parasite biochemistry are being exposed by our exploration of the drugs. Further work on these matters with special reference to mefloquine will be carried out during the coming year.

Studies will also be extended on the development of slow-release preparations of selected drugs.

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9 APPENDICES

- Tables 1 through 14 The causal prophylactic potential of new Walter Reed compounds in rodent malaria model. Included are results of 110 Walter Reed 8-amino-quinolines plus 5 from other sources, 6-naphthyridines and 18 miscellaneous compounds. These data include an interpretation of minimum fully curative dosage (MFCD) presented in Schmidt's Final Report 1976.
- Tables 15 through 38 The results of preliminary screening of compounds in causal prophylactic activity in the rodent screen.
- Tables 39 through 53 Summary of data from causal prophylactic test in P. y. nigeriensis
- Table 54 The relationship between parasitaemia and catheptic activity in P. berghei-infected mouse erythrocytes
- Figure 1 A comparison of the rate of acquisition of resistance to mefloquine by the chloroquine-sensitive P. berghei N strain and the NS line which has a low level of resistance to chloroquine.
- Figure 2 The acquisition of resistance to mefloquine by P. berghei NS line passaged under drug pressure (mefloquine 60 mg/kg sc at time of each passage), and its reversion to sensitivity on the release of drug selection pressure.
- Figure 3 Rate of acquisition by P. berghei N strain of resistance to mefloquine, pyrimethamine and sulphaphenazole when the drugs are used alone.
- Figure 4 Influence of combining mefloquine with pyrimethamine on the rate of acquisition of resistance to each drug by P. berghei in consecutive passages.
- Figure 5 Influence of combining mefloquine with sulphaphenazole on the rate of acquisition of resistance to each drug by P. berghei N strain in consecutive passages.
- Figure 6 Influence of combining mefloquine with primaquine on the rate of acquisition of resistance to each drug by P. berghei in consecutive passages.
- Figure 7 Blood schizontocidal action of drug mixtures against P. berghei N strain in the "4-day test".

GROUP								
8-aminoquinolines			I Primaquine derivatives		(a) variations in 1, 2, 3, 4 positions			
LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary d
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1370	2975E19	AG66475	2.2	66-132	1.0	66-132	1.0	Primaquine
1269 }	5990AC	BG60018	2.1	Inactive at MTD	-	63-126	1.1	MTD sc 63
1272 }		AG99266		Inactive at MTD				
1377 }		AG99266		Inactive at MTD				
1289 }	182234AA	BE10198	2.9	8.7-39	3.3	<8.7*	>11.4	
1326 }	182234AD	BE17580	2.8	28-84	1.8			
1322 }	211814AB	BE12905	2.9	0.9-2.9	52.1			
1379 }				2.9-8.7	26.0			
1273 }	181023AE	BD57427	2.1	63-210	0.7	21-63*	2.4	
1373 }	181023AG	BE50003	2.1	63-210	0.7			
1291	210550AA	BE11597	2.4	72-240	0.6	>MTD	-	MTD po 171
1402	228002AA	BG58189	1.9	<5.7	>17.4			
1387 }	219874AA	BE79802	2.5	2.5-7.5	19.8	<0.4		
1451 }		ZN42821		>250*				
1452	215733AA	ZN43328	2.5	Inactive at 250	-	Inactive at MTD	-	MTD po 75
1302	208442AA	ED57981	2.2	66-132	1.0	<60*	>1.7	
1404	228335AA	BG60689	2.0	20-60	2.5			
1268 }	183489AD	BD56671	2.5	Inactive at 1875	-			
1280 }	183489AE	BD57552	2.5	1875-2500	0.05			
1323	214703AA	BE15040	2.0	200-600	0.25			

MFED = minimum fully effective dose
(daily)

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = prim

2

TABLE 1

I. Primaquine derivatives (a) variations in 1, 2, 3, 4 positions

Dose/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.2	66-132	1.0	66-132	1.0	Primaquine	1.1	1.0
2.1	Inactive at MTD	-			} MTD sc 63	1.05-2.1	0.5-1.04
	Inactive at MTD						
	Inactive at MTD		63-126	1.1			
2.9	8.7-39	3.3				7.3-14.5	0.08-0.15
2.8	28-84	1.8					
2.9	0.9-2.9	52.1				9.7	0.11
	2.9-8.7	26.0	<8.7*	>11.4			
2.1	63-210	0.7				0.5-1.1	1.1-2.1
2.1	63-210	0.7	21-63*	2.4			
2.4	72-240	0.6				2.4	0.45
1.9	<5.7	>17.4	>MTD	-	MTD po 171	na	
2.5	2.5-7.5	19.8				1.25	0.9
	>250*	<0.4					
2.5	Inactive at 250	-	Inactive at MTD	-	MTD po 75	0.63-1.25	0.9-1.7
2.2	66-132	1.0				1.6-3.2	0.3-0.7
2.0	20-60	2.5	<60*	>1.7		na	
2.5	Inactive at 1875	-				2.5-5.0	0.2-0.4
2.5	1875-2500	0.05					
2.0	200-600	0.25				2∅	

Active dose

MFCd = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

I (a) continued

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary data)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1361	216893AA	BE19477	1.9	> 570	< 0.2			
1472	229427AA	BG70550	2.0	Inactive at 200*	-	> 200	< 0.5	
1355	219382AA	BE71226	2.1	63-126	1.0			
1356	219783AA	BE75948	1.7	Inactive at 1020	-			
1357	219784AA	BE75939	1.8	108-180	0.7			
1259	199507AB	BD24062	1.9	> MTD	-			MTD sc 57
1411	225374AA	BG37591	2.2	> MTD	-	< 66*	> 1.5	MTD sc 6.6
1305 }	211532AA	BE12567	1.9	> 570	< 0.2			Residual activity
1448 }		ZN41048		Inactive at 190	-	Inactive at 190	-	
1307	182232AC	BE08456	2.5	> 750	< 0.1			
1382	216100AA	BE17491	1.7	> 170	< 0.6			Residual activity
1470	224097AA	ZN43953	2.0	> 200*	< 0.5	> 200*	< 0.5	
1345 }	215295AA	BE16378	1.6	Inactive at 480				
1381 }				Inactive at 480				
1438	225448	BG37402	1.9	< 57*	> 1.7	< 57*	> 1.7	
1384	218676AA	BE55820	2.4	24-72	2.1			
1400	228000AA	BG58367	2.2	> MTD	-	< 69*	> 1.4	MTD sc 66
1138 }	106147AD	AY77897	2.2	22-66	2.3			
1432 }				66-220*	0.7	< 66*	> 1.5	
1383	217124AA	BE43759	1.8	54-108	1.2			

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = pri

TABLE 2

2

mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
9	>570	<0.2				190	-
0	Inactive at 200*	-	>200	<0.5		na	
1	63-126	1.0				na	
7	Inactive at 1020	-				na	
8	108-180	0.7				na	
9	>MTD	-			MTD sc 57	190	
2	>MTD	-	<66*	>1.5	MTD sc 6.6	na	
9	>570	<0.2			Residual activity	0.48-0.95	1.2-2.3
	Inactive at 190	-	Inactive at 190	-			
5	>750	<0.1				1.9-2.5	0.4-0.6
7	>170	<0.6			Residual activity	0.43-0.85	1.3-2.6
0	>200*	<0.5	>200*	<0.5		0.5-1.0	1.1-2.2
6	Inactive at 480					0.4-0.8	1.4-2.8
	Inactive at 480						
9	<57*	>1.7	<57*	>1.7		0.23-0.48	2.3-4.8
4	24-72	2.1				2.40 24tox	
2	>MTD	-	<69*	>1.4	MTD sc 66	na	
2	22-66	2.3				3.3	0.3
	66-220*	0.7	<66*	>1.5			
8	54-108	1.2				0.9	1.2

tive dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

I (a) continued

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1386	217154AA	BE67204	2.0	60-120	1.1			
1267 } 1435 }	205439AA	BD54195	1.8	1.8-5.4 54-180*	27.5 1.0	5.4-18*	8.5	
1053 } 1316 }	F 142		2.2	Inactive at MTD Inactive at MTD				MTD sc 220
1056	157835	AW23379	2.2	1320-2200	0.06			Residual activity
1417 } 1446 }	228708AA	BG66798	2.1	< 21*	> 4.7	< 63 *	> 1.6	
	228708AB	BG70756	2.1	< 63*	> 1.6	> 63	< 1.6	LD ₁₀₀ po < 210
1414 } 1445 }	228583AA	BG63664	2.3	> 23	< 4.3			LD ₆₆ sc/po ~ 69; LD ₁₀₀
	228583AB	BG70729	2.3			< 69	> 1.4	LD ₁₀₀ sc < 69; LD ₁₀₀
1407	219130AA	BE58643	2.0	< 60 *	> 1.7	60-200 *	2.2	
1476	230388AA	BG81580	2.4	Inactive at 240	-	< 72 *	> 1.4	LD ₁₀₀ po < 240
1454	216804AA	ZN43426	2.0	< 60 *	> 1.7			LD ₁₀₀ po < 60

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = prim

TABLE 3

base/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.0	60-120	1.1				1-2	0.6-1.1
1.8	1.8-5.4 54-180*	27.5 1.0	5.4-18*	8.5		1.8	0.6
2.2	Inactive at MTD Inactive at MTD				MTD sc 220	na	
2.2	1320-2200	0.06			Residual activity	na	
2.1	< 21*	> 4.7	< 63 *	> 1.6			
2.1	< 63*	> 1.6	> 63	< 1.6	LD ₁₀₀ po < 210		
2.3	> 23	< 4.3			LD ₆₆ sc/po ~ 69; LD ₁₀₀ sc/po < 230		
2.3			< 69	> 1.4	LD ₁₀₀ sc < 69; LD ₁₀₀ po < 230		
2.0	< 60 *	> 1.7	60-200 *	2.2		na	
2.4	Inactive at 240	-	< 72 *	> 1.4	LD ₁₀₀ po < 240	na	
2.0	< 60 *	> 1.7			LD ₁₀₀ po < 60	0.25-1.0	1.1-4.4

active dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

8-aminoquinolines

I Primaquine derivatives. (b) variations on terminal amino of side chain

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary data)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1197	189294AB	BE46719	2.7	81-270	0.6			
1202	188303AA	BB45543	1.8	Inactive at 1800	-			
1082 } 1378 }	161085AB	AX26820	1.0	Inactive at 30 30-60	- 2.2			
1282	182230AB	BD58040	2.5	> 2500	< 0.04			
1257	181721AB	BD27161	1.9	Inactive at 1900	-			
1304	181517AB	BE12370	2.3	69-230	0.7			
1058	F156		2.4	72-240	0.6			

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = prim

TABLE 4

2

I Primaquine derivatives. (b) variations on terminal amino of side chains and other positions.

base/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.7	81-270	0.6				na	
1.8	Inactive at 1800	-				na	
1.0	Inactive at 30	-				2.5	0.4
	30-60	2.2					
2.5	> 2500	< 0.04				na	
1.9	Inactive at 1900	-				na	
2.3	69-230	0.7				na	
2.4	72-240	0.6				na	

Effective dose

MFCD = minimum fully curative dose
(daily mg/kg po)

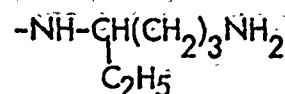
PI = primaquine index

GROUP

8-aminoquinolines

I Primaquine derivatives

(c) variations on



IV. No.	WR No.	BN No.	$\mu\text{M base/mg}$	s.c.		p.o.		Comments (toxicity, preliminary data)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1392	215761AA	BE16967	1.9	19-57	2.6	<57*	>1.7	LD ₁₀₀ sc/po 8h
1393	226426AA	BG45208	2.7	2.7-8.1	18.3			
1391	226296AA	BG44452	2.4	2.4-7.2	20.6	<72*	>1.4	
1409	226762AA	BG47293	2.5	>150*	<0.7	Inactive at 250*	-	

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine

2

TABLE 5

Primaquine derivatives		(c) variations on		$\begin{array}{c} \text{-NH-CH(CH}_2\text{)}_3\text{NH}_2 \\ \\ \text{C}_2\text{H}_5 \end{array}$			
Dose/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
1.9	19-57	2.6	<57*	>1.7	LD ₁₀₀ sc/po 81	0.24	4.6
2.7	2.7-8.1	18.3				na	
2.4	2.4-7.2	20.6	<72*	>1.4		na	
2.5	>150*	<0.7	Inactive at 250*	-		na	

active dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

8-aminoquinolines

II Based on isopentaquine

LIV. No.	WR. No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1375 }	6020AC	BE 21066	2.0			\sim 200	\sim 0.5	MTD po 200
1374 }	6020AD	BE20783	2.0			$>$ MTD	-	MTD po 156
1371	6027AO	AG75828	3.7			111-222	0.6	
1303	21815AA	BE08527	1.9	$>$ 57	$<$ 1.7			Residual activity
1290	210551AA	BE11588	2.2	$>$ MTD	-			MTD sc 220

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = pri

TABLE 6

2

Based on isopentaquine

Dose/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.0			~ 200	~ 0.5	MTD po 200	}	na
2.6			> MTD	-	MTD po 156		
3.7			111-222	0.6		3.70	
4.9	> 57	< 1.7			Residual activity	19	0.06
9.2	> MTD	-			MTD sc 220	22	0.05

Active dose

MFC D = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

8 aminoquinolines

III Based on quinocide

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary d
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1385	152149AB	BE66770	2.8	> MTD	-			MTD sc 280
1325	215296AA	BE16369	2.1	6.3-21	7.3			
1388	222671AA	BG11891	2.1	63-126	1.0			
1413	228456AA	BG62807	2.4	< 7.2* >	13.8			LD ₁₀₀ sc/po < 72
1439	221527AB	BG48898	2.5	< 7.5* >	13.2			LD ₁₀₀ sc 25; po 75
1408	226937AA	BG55008	2.5	75-150*	0.9	75-250*	0.6	LD ₆₆ po ~ 250
1412	228457AA	BG62790	2.5	> 75 *	< 1.3	75-250*	0.6	LD ₁₀₀ sc < 250
1389	222890AA	BG13831	1.8	Inactive at 540	-			
1421	229238AA	BG70112	2.0	Inactive at 200*	-	> 200*	< 0.5	
1348	218335AA	BE66930	2.1	21-63	2.4			
1437				21-63	2.4	< 63 *	> 1.6	

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = pri

2

TABLE 7

III Based on quinocide

Dose/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.8	> MTD	-			MTD sc 280	2.8	0.4
2.1	6.3-21	7.3				0.26	4.2
2.1	63-126	1.0				0.53-1.1	0.05-2.1
2.4	< 7.2* >	13.8			LD ₁₀₀ sc/po < 72	}	0.3-1.25 0.9-3.5
2.5	< 7.5* >	13.2			LD ₁₀₀ sc 25; po 75		
2.5	75-150*	0.9	75-250*	0.6	LD ₆₆ po ~ 250		
2.5	> 75* <	1.3	75-250*	0.6	LD ₁₀₀ sc < 250		
1.8	Inactive at 540	-				0.9-1.8	0.6-1.2
2.0	Inactive at 200*	-	> 200*	< 0.5		na	
2.1	21-63	2.4				}	1.05-2.1 0.5-1.04
	21-63	2.4	< 63 *	> 1.6			

Effective dose

MFC D = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

1

GROUP

8-aminoquinolines

IV Based on pentaquine

IV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary data)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1376	6021AK	BE20907	2.5			> 250	< 0.4	
1372	127854AC	BE20087	2.6			78-156	0.9	
1343	211674AB	BE20587	2.2	inactive at 660	-			
1256	49577AE	BD27698	1.8	> MTD	-			MTD sc 54
1354	194343AA	BC06452	1.9	114-190	0.7			
1226	196469AA	BC51797	1.6	> 160	< 0.6			Residual activity
1360	218670AB	BE59088	1.9	> MTD	-			MTD sc 190
1284 }	203608AA	BD27661	1.4	1.4-4.2	35.4			
1449 }		ZN42125		> 140 *	< 0.7	42-140*	1.1	
1283 }	203607AA	BD27652	1.4	42-140	1.1			
1434 }				42-140*	1.1	< 42*	> 2.4	
1255 }	202437AA	BD26164	1.6	16-48	3.1			
1433 }				< 51 *	> 1.9	< 51 *	> 1.9	

MFED = minimum fully effective dose
(daily)

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = prime

TABLE 8

Z

IV Based on pentaquine

Dose/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.5			> 250	< 0.4		na	
2.6			78-156	0.9		1.3-2.6	0.4-0.9
2.2	Inactive at 660	-				na	
1.8	> MTD	-			MTD sc 54	18Ø	
1.9	114-190	0.7				19	0.06
1.6	> 160	< 0.6			Residual activity	na	
1.9	> MTD	-			MTD sc 190	na	
1.4	1.4-4.2	35.4				14	0.08
	> 140 *	< 0.7	42-140*	1.1			
1.4	42-140	1.1				14	0.08
	42-140*	1.1	< 42*	> 2.4			
1.6	16-48	3.1				5.3-16	0.1-0.2
	< 51 *	> 1.9	< 51 *	> 1.9			

Active dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

8-aminoquinolines

V. Sidechain on 8 with 6 carbons before NH_2 (a)

LIV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary data)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1380	212624AA	BE13822	1.9	57-114	1.1			
1416	228710AA	BG66412	2.3	<23 *	>4.3			LD_{50} sc/u 23; LD_{100} <
1350	211208AA	BE20005						Not sent
1453	212223AA	ZN43391	2.4	72-240*	0.6	72-240*	0.6	
1428	212579AB	BG48969	2.1	63-210*	0.7			
1410	226899AB	BG52623	2.4					LD_{100} sc/po <72

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primary

2

TABLE 9

V. Sidechain on 8 with 6 carbons before NH_2 (a)

base/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
1.9	57-114	1.1				0.95-1.9	0.6-1.1
2.3	<23 *	>4.3			LD ₅₀ sc \sim 23; LD ₁₀₀ <69 Not sent	na	
2.4	72-240*	0.6	72-240*	0.6		0.6-2.4	0.5-1.8
2.1	63-210*	0.7				0.26-0.52	2.1-4.2
2.4					LD ₁₀₀ sc/po <72	na	

Effective dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

8-aminoquinolines

V Sidechain on 8 with 6 carbons before NH₂ (b)

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary d
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1180	6025AO	BE21431	2.7	Inactive at 810	-			
1181	6026AI	AG75499		Inactive at MTD	-			MTD sc 240
1425	6026AD	BG14463	2.4					Not tested
1431	6026AI	AG75499		72-240*	0.6	<72*	>1.4	
1427	211666AB	BG11417	2.4	<72 *	>1.4			
1398	227495AA	BG56738	2.3	69-230*	0.7	>MTD *		LD ₆₆ sc 230; MTD po
1429	226257AA	BG44425	2.0	<60 *	>3.3			
1403	228327AA	BG60698	1.9	114-190	0.7	57-190*	0.8	
1426	226292AA	BG44541	2.3					LD ₁₀₀ sc <69

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = pri

TABLE 10

2

V. Sidechain on 8 with 6 carbons before NH_2 (b)

base/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.7	Inactive at 810	-				na	
	Inactive at MTD	-			MTD sc 240		
2.4	72-240*	0.6	<72*	>1.4	Not tested	1.2	0.9
2.4	<72*	>1.4				2.4	0.45
2.3	69-230*	0.7	>MTD *		LD ₆₆ sc 230; MTD po 69	na	
2.0	<60*	>3.3				na	
1.9	114-190	0.7	57-190*	0.8		na	
2.3					LD ₁₀₀ sc <69	na	

Active dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

8-aminoquinolines

VI Piperazine linkages on position 8

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary d
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1399	227681AA	BG56612	2.0	120-200	0.6			Activity principally resid
1154 } 1362 }	BW349C59		1.7	17-51 17-51	2.9 2.9			
1442	229406AA	BG70603	1.9	Inactive at 114*	-	Inactive at 190*	-	
1477	230395AA	BG81599	1.8	Inactive at 180*	-	Inactive at 180*	-	
1478	230394AA	BG81606	1.9	Inactive at 190*	-	Inactive at 190*	-	
1440	229431AA	BG70578	2.0	>120 *	<0.8	Inactive at 200*	-	
1441	229397AA	BG70596	1.9	>114 *	<0.9	>190*	<0.5	
1443	229396AA	BG70630	1.9	>114 *	<0.9	Inactive at 190*	-	
1444	229398AA	BG70658	1.9	Inactive at 114*	-	Inactive at 190*	-	
1471	229429AA	BG70667	1.8	Inactive at 180*	-	Inactive at 180*	-	

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = prin

2

TABLE 11

VI Piperazine linkages on position 8

Dose/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.0	120-200	0.6			Activity principally residual	na	
1.7	17-51	2.9				na	
	17-51	2.9					
1.9	Inactive at 114*	-	Inactive at 190*	-		na	
1.8	Inactive at 180*	-	Inactive at 180*	-		na	
1.9	Inactive at 190*	-	Inactive at 190*	-		na	
2.0	>120 *	<0.8	Inactive at 200*	-		na	
1.9	>114 *	<0.9	>190*	<0.5		na	
1.9	>114 *	<0.9	Inactive at 190*	-		na	
1.9	Inactive at 114*	-	Inactive at 190*	-		na	
1.8	Inactive at 180*	-	Inactive at 180*	-		na	

Effective dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

8-aminoquinolines

VII Miscellaneous types

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary data)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1279	179443AC	BD57436	5.3	Inactive at 1590	-			
1270	189296AA	BB46595	3.0	Inactive at 900	-			
1271	189296AB	BC09186		Inactive at 900	-			
1262	206027AA	BD54471	3.1	> MTD	-			MTD sc 310
1473	4396AR	BG44621	2.1	Inactive at MTD*	-	Inactive at MTD*	-	MTD sc 60; po 30
1390	211533AC	BG38034	2.0	Inactive at 300	-	Inactive at 200	-	MTD sc 300
1436	211533AB	BE12601	2.0	Inactive at 200*	-	Inactive at 60*	-	LD ₁₀₀ po < 200
1344	211816AA	BE20630	2.5	75-150	0.9			
1346	29594AC	BE20014	3.1	31-93	1.6			
1184	7312AI	BB47761	2.3	Inactive at 2300	-			
1264	29634AB	BD04622	1.9	57-190	0.8			
1401	227988AA	BG58447	2.0	Inactive at 600	-	60-200*	0.8	
1419	229011AA	BG67099	2.0	60-200*	0.8	> 200*	< 0.5	LD ₅₀ sc ~ 200
1314	213640AA	BE09999	2.0	> 600	< 0.2			
1347	218336AA	BE66832	2.1	210-630	0.2			
1334	201678AB	BE13304	2.1	21-63	2.4			
1447		ZN40130		66-220*	0.7	< 66*	> 1.5	
1420	229092AA	BG68354	2.9	Inactive at 290*	-	Inactive at 290*	-	
1482	230212AA	BG80994	2.2	Inactive at 220*	-	Inactive at 220*	-	
1043	Ni 147/36	Dann	2.7	8.1-27	5.6			
1044	Ba138/11		2.6	26-78	1.9			

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = prim

TABLE 12

2

VII Miscellaneous types

base/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
5.3	Inactive at 1590	-				na	
3.0	Inactive at 900	-				na	
	Inactive at 900	-					
3.1	> MTD	-			MTD sc 310	3.1Ø	
2.1	Inactive at MTD*	-	Inactive at MTD*	-	MTD sc 60; po 30	na	
2.0	Inactive at 300	-	Inactive at 200	-	MTD sc 300	1.0	1.1
2.0	Inactive at 200*	-	Inactive at 60*	-	LD ₁₀₀ po < 200		
2.5	75-150	0.9				25	0.04
3.1	31-93	1.6				3.1	0.35
2.3	Inactive at 2300	-				23Ø	-
1.9	57-190	0.8				19Ø	-
2.0	Inactive at 600	-	60-200*	0.8		na	
2.0	60-200*	0.8	> 200 *	< 0.5	LD ₅₀ sc ~ 200	na	
2.0	> 600	< 0.2				na	
2.1	210-630	0.2				na	
2.1	21-63	2.4				21Ø	
	66-220*	0.7	< 66 *	> 1.5			
2.9	Inactive at 290*	-	Inactive at 290*	-		na	
2.2	Inactive at 220*	-	Inactive at 220*	-		na	
2.7	8.1-27	5.6				na	
2.6	26-78	1.9				na	

Effective dose

MFCD : minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

Naphthyridines

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary d
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1485	206287AB	BG81759	2.3	Inactive at 230*	-	Inactive at 230*	-	Residual activity only LD ₃₀ sc ~ 160 LD ₃₀ sc ~ 990 LD ₃₀ sc ~ 1280
1487	222119	BG81740	2.2	Inactive at 220*	-			
1278	206218AA	BD54766	1.5	>750	<0.1			
1287	210446AA	BE10983	1.6	Inactive at LD ₃₀	-			
1286	210447AA	BE10965	3.3	Inactive at LD ₃₀	-			
1288	210434AA	BE11024	4.3	Inactive at LD ₃₀	-			

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = prim

2

TABLE 13

base/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.3	Inactive at 230*	-	Inactive at 230*	-		na	
2.2	Inactive at 220*	-				na	
1.5	>750	<0.1			Residual activity only	na	
1.6	Inactive at LD ₃₀	-			LD ₃₀ sc ~ 160	na	
3.3	Inactive at LD ₃₀	-			LD ₃₀ sc ~ 990	na	
4.3	Inactive at LD ₃₀	-			LD ₃₀ sc ~ 1280	na	

Effective dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

GROUP

Miscellaneous compounds

LIV. No.	WR No.	BN No.	μ M base/mg	s.c.		p.o.		Comments (toxicity, preliminary data)
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1484	230284AA	BG81222	2.3	Inactive at 230*	-	Inactive at 230*	-	LD ₃₃ po ~ 210 LD ₃₃ po ~ 230
1483	230225AA	BG81035	2.1	Inactive at 210*	-	Inactive at 210*	-	
1486	230621AA	BG83191	2.3	Inactive at 230*	-	> 230 *	< 0.4	
1479	230387AA	BG81615	2.9	< 290	> 0.3	Inactive at 290*	-	
1480	230386AA	BG81624	2.2	Inactive at 220*	-	> 220 *	< 0.4	
1474	206513AB	BG79017	2.1	> 210 *	< 0.5	> 210 *	< 0.5	
1481	230216AA	BG80967	1.7	Inactive at 170*	-	Inactive at 170*	-	
1430	129577AC	AW41662	2.0	Inactive at 200*	-	Inactive at 200*	-	
1422	194965AD	BG43991	2.7	< 81 *	> 1.2	> 270 *	< 0.4	
1415	228769AA	BG66403	1.6	Inactive at 160*	-	Inactive at 160*	-	
1423	225449AA	BG37573	2.8	< 84 *	> 1.2	< 84 *	> 1.2	
1405	220594AA	BE84652	2.1	> 126 *	> 0.8	Inactive at 210*	-	
1406	220679AA	BE96303	2.3	< 138 *	> 0.7	Inactive at 230*	-	Guanidine derivative Diamidine
1418	229046AA	BG67179	2.6	78-260*	0.6	Inactive at 260*	-	
1394	226626AA	BG46714	2.4	2.4-7.2	20.6	72-240*	0.6	
1395	199361AC	BG47168	3.0	3.0-9.0	16.5	< 90 *	> 1.1	
1203	182058	AY98947	3.2	3.2-9.6	15.5			
1251	190830	BD29165	2.2	66-220	0.7			

MFED = minimum fully effective dose
(daily)MFCD = minimum fully curative dose
(daily mg/kg po)

PI = prim

TABLE 14

2

Compounds

Dose/mg	s.c.		p.o.		Comments (toxicity, preliminary data, etc.)	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.		M.F.C.D.	P.I.
2.3	Inactive at 230*	-	Inactive at 230*	-	LD ₃₃ po ~ 210 LD ₃₃ po ~ 230	na	
2.1	Inactive at 210*	-	Inactive at 210*	-		na	
2.3	Inactive at 230*	-	> 230 *	< 0.4		na	
2.9	< 290	> 0.3	Inactive at 290*	-		na	
2.2	Inactive at 220*	-	> 220 *	< 0.4		na	
2.1	> 210 *	< 0.5	> 210 *	< 0.5		na	
1.7	Inactive at 170*	-	Inactive at 170*	-		na	
2.0	Inactive at 200*	-	Inactive at 200*	-		na	
2.7	< 81 *	> 1.2	> 270 *	< 0.4		na	
1.6	Inactive at 160*	-	Inactive at 160*	-		na	
2.8	< 84 *	> 1.2	< 84 *	> 1.2	Guanidine derivative Diamidine	na	
2.1	> 126 *	> 0.8	Inactive at 210*	-		na	
2.3	< 138 *	> 0.7	Inactive at 230*	-		na	
2.6	78-260*	0.6	Inactive at 260*	-		na	
2.4	2.4-7.2	20.6	72-240*	0.6		na	
3.0	3.0-9.0	16.5	< 90 *	> 1.1		na	
3.2	3.2-9.6	15.5				32 Ø	
2.2	66-220	0.7				22 Ø	

Active dose

MFCD = minimum fully curative dose
(daily mg/kg po)

PI = primaquine index

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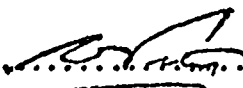
TABLE 15

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	µM Base/Kg	Comment
1370	2975	AG64745	po	1.0				✓	2.2	Primaquine
				10.0			✓		22.0	
				30.0		✓			66.0	
				60.0	✓				132.0	
				100.0	✓				220.0	
1371	6027	AG75828	po	1.0				✓	3.7	4-methyl isopentaquine
				10.0				✓	37.0	
				30.0		✓			111.0	
				60.0	✓				222.0	
				100.0	✓				370.0	
1372	127854	BE20087	po	1.0				✓	2.6	4-methyl pentaquine
				10.0				✓	26.0	
				30.0		✓			78.0	
				60.0	✓				156.0	
				100.0	✓				260.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

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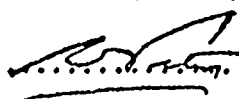
TABLE 16

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1373	181023	BE50003	po	1.0				✓	2.1	4-methyl primaquine
				10.0			✓		21.0	
				30.0	✓				63.0	
				60.0	✓				126.0	
				100.0	✓				210.0	~ LD ₃₃
1374	6020AD	BE20783	po	1.0				✓	2.6	isopentaquine oxalate
				10.0			✓		26.0	
				30.0			✓		78.0	
				60.0		✓			156.0	
				100.0	✓				260.0	~ LD ₆₆
1375	6020AC	BE21066	po	30.0		✓			60.0	isopentaquine diphosphate
				60.0		✓			120.0	
				100.0	✓				200.0	
1376	6021	BE20907	po	1.0				✓	2.5	Pentaquine
				10.0			✓		25.0	
				30.0	✓				75.0	
				100.0	✓				250.0	~ LD ₃₃

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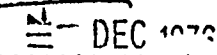
TABLE 17

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1377	5990	AG99266	sc	10.0				✓	221.0	
				30.0				✓	63.0	\sim LD ₃₃
				100.0					210.0	$>$ LD ₁₀₀
1377	5990	AG99266	po	3.0				✓	6.3	
				30.0			✓		63.0	
				60.0	✓				126.0	
1378	161085	AX26820	sc	10.0				✓	10.0	
				30.0		✓			30.0	
				100.0	✓				100.0	\sim LD ₃₃
1378	161085	AX26820	po	3.0			✓		3.0	
				30.0	✓				30.0	
1379	211814	BE12905	sc	1.0		✓			2.9	
				10.0	✓				29.0	
				30.0	✓				87.0	
				100.0					290.0	$>$ LD ₁₀₀
1379	211814	BE12905	po	3.0	✓				8.7	
				30.0	✓				87.0	

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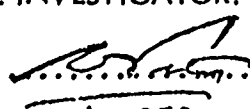
TABLE 18

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1380	212624	BE13822	sc	10.0				✓	19.0	
				30.0			✓		57.0	
				100.0	✓				190.0	
1381	215295	BE16378	sc	10.0				✓	16.0	
				30.0				✓	48.0	
				100.0			✓		160.0	3/3 Patent but delayed
				300.0			✓		480.0	
1382	216100	BE17491	sc	1.0				✓	1.7	
				10.0				✓	17.0	
				30.0				✓	51.0	
				100.0	✓				170.0	
1383	217124	BE43759	sc	1.0				✓	1.8	
				10.0			✓		18.0	
				30.0	✓				54.0	
				100.0	✓				180.0	

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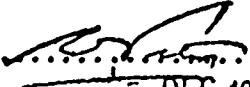
TABLE 19

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1384	218676	BE55820	sc	1.0				✓	2.4	
				10.0	✓				24.0	
				30.0	✓				72.0	
				100.0					240.0	>LD ₁₀₀
1385	152149	BE66770	sc	30.0			✓		84.0	
				100.0		✓			280.0	
				300.0					840.0	>LD ₁₀₀
1386	217154	BE67204	sc	1.0				✓	2.0	
				10.0		✓			20.0	
				30.0	✓				60.0	
				100.0	✓				200.0	
1387	219874	BE79802	sc	1.0				✓	2.5	
				10.0	✓				25.0	
				30.0	✓				75.0	
				100.0					250.0	>LD ₁₀₀
1388	222671	BG11891	sc	30.0			✓		63.0	
				60.0		✓			126.0	
				100.0	✓				210.0	

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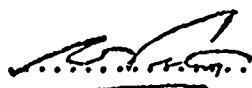
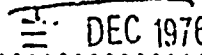
TABLE 20

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1389	222890	BG13831	sc	30.0			✓		54.0	
				100.0		✓			180.0	
1389	222890	BG13831	po	30.0				✓	54.0	
				100.0				✓	180.0	
1390	211533	BG38034	sc	30.0			✓		60.0	
				100.0			✓		200.0	
1390	211533	BG38034	po	30.0				✓	60.0	
				100.0				✓	200.0	
1391	226296	BG44452	sc	1.0			✓		2.4	
				10.0	✓				24.0	
				30.0	✓				72.0	\sim LD ₆₆
				100.0					240.0	$>$ LD ₁₀₀
1391	226296	BG44452	po	30.0	✓				72.0	\sim LD ₆₆
				100.0					240.0	$>$ LD ₁₀₀
1392	215761	BE16967	sc	1.0			✓		1.9	
				10.0	✓				19.0	
				30.0	✓				57.0	
				100.0	✓				190.0	

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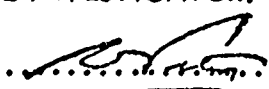
TABLE 21

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1392	215761	BE16967	po	30.0	✓				57.0	
				100.0	✓				190.0	
1393	226426	BG45208	sc	1.0	✓				2.7	
				10.0	✓				27.0	
				30.0					81.0	> LD ₁₀₀
				100.0					270.0	> LD ₁₀₀
1393	226426	BG45208	po	30.0					81.0	> LD ₁₀₀
				100.0					270.0	> LD ₁₀₀
1394	226626	BG46714	sc	1.0			✓		2.4	
				10.0	✓				24.0	
				30.0	✓				72.0	
				100.0	✓				240.0	
1394	226626	BG46714	po	30.0		✓			72.0	
				100.0	✓				240.0	
1395	199361	BG47168	sc	1.0			✓		3.0	
				10.0	✓				30.0	
				30.0	✓				90.0	
				100.0	✓				300.0	

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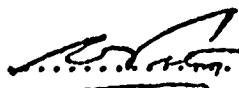
TABLE 22

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1395	199361	BG47168	po	30.0	✓				90.0	
				100.0	✓				300.0	
1396	206891	BG47462	sc	1.0				✓	2.9	
				10.0				✓	29.0	
				30.0	✓				87.0	
				100.0	✓				290.0	
1396	206891	BG47462	po	30.0		✓			87.0	
				100.0	✓				290.0	
1397	216693	BG47239	sc	30.0				✓	111.0	
				100.0				✓	370.0	
1397	216693	BG47239	po	30.0	✓				111.0	
				100.0	✓				370.0	
1398	227495	BG56738	sc	30.0		✓			69.0	
				100.0	✓				230.0	\sim LD ₆₆
1398	227495	BG56738	po	30.0		✓			69.0	\sim LD ₃₃
				100.0					230.0	$>$ LD ₁₀₀

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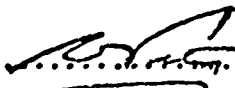
TABLE 23

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x l	1	2	3	4	μ M Base/Kg	Comment
1399	227681	BG56612	sc	30.0				✓	60.0	
				100.0	✓				200.0	
1399	227681	BG56612	po	30.0	✓				60.0	
				100.0	✓				200.0	
1400	228000	BG58367	sc	30.0			✓		69.0	
				100.0	✓				230.0	\sim LD ₃₃
1400	228000	BG58367	po	30.0	✓				69.0	
				100.0					230.0	$>$ LD ₁₀₀
1401	227988	BG58447	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1401	227988	BG58447	po	30.0		✓			60.0	
				100.0	✓				200.0	
1402	228002	BG58189	sc	30.0	✓				60.0	
				60.0	✓				120.0	
1402	228002	BG58189	po	30.0		✓			60.0	\sim LD ₃₃
				100.0					200.0	$>$ LD ₁₀₀

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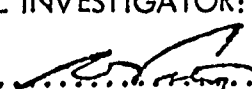
TABLE 24

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	µM Base/Kg	Comment
1403	228327	BG60698	sc	30.0			✓		57.0	
				100.0	✓				190.0	
1403	228327	BG60698	po	30.0			✓		57.0	
				100.0	✓				190.0	
1404	228335	BG60689	sc	30.0	✓				63.0	
				100.0	✓				210.0	
1404	228335	BG60689	po	30.0	✓				63.0	
				100.0	✓				210.0	
1405	220594	BE84652	sc	30.0			✓		63.0	
				60.0		✓			126.0	
1405	220594	BE84652	po	30.0				✓	63.0	
				100.0				✓	210.0	
1406	220679	BE96303	sc	30.0	✓				69.0	
				60.0	✓				138.0	
1406	220679	BE96303	po	30.0				✓	69.0	
				100.0				✓	230.0	

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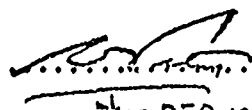
TABLE 25

Category 1 - ? Fully active = 0/3 Patent
 2 - ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x l	1	2	3	4	μ M Base/Kg	Comment
1407	219130	BE58643	sc	30.0	✓				60.0	
				60.0	✓				120.0	
1407	219130	BE58643	po	30.0		✓			60.0	
				100.0	✓				200.0	
1408	226937	BG55008	sc	30.0			✓		75.0	
				60.0	✓				150.0	
1408	226937	BG55008	po	30.0			✓		77.5	
				100.0	✓				250.0	\sim LD ₆₆
1409	226762	BG47293	sc	30.0		✓			75.0	
				60.0		✓			150.0	
1409	226762	BG47293	po	30.0				✓	75.0	
				100.0				✓	250.0	
1410	226899	BG52623	sc	30.0					72.0	> LD ₁₀₀
				60.0					144.0	> LD ₁₀₀
1410	226899	BG52623	po	30.0					72.0	> LD ₁₀₀
				100.0					240.0	> LD ₁₀₀

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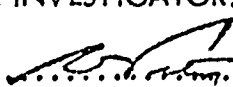
TABLE 26

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1411	225374	BG37591	sc	30.0	✓				66.0	
				100.0					220.0	> LD ₁₀₀
1411	225374	BG37591	po	30.0	✓				66.0	
				100.0	✓				220.0	
1412	228457	BG62790	sc	10.0		✓			25.0	
				30.0		✓			75.0	
				100.0					250.0	> LD ₁₀₀
1412	228457	BG62790	po	30.0		✓			75.0	
				100.0	✓				250.0	
1413	228456	BG62807	sc	3.0	✓				7.2	
				10.0	✓				24.0	
				30.0					72.0	> LD ₁₀₀
				100.0					240.0	> LD ₁₀₀
1413	228456	BG62807	po	30.0					72.0	> LD ₁₀₀
				100.0					240.0	> LD ₁₀₀

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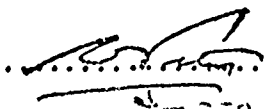
TABLE 27

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1414	228583	BG63644	sc	3.0		✓			6.9	
				10.0		✓			23.0	
				30.0	✓				69.0	\sim LD ₆₆
				100.0					230.0	$>$ LD ₁₀₀
1414	228583	BG63644	po	30.0	✓				69.0	\sim LD ₆₆
				100.0					230.0	$>$ LD ₁₀₀
1415	228769	BG66403	sc	10.0				✓	16.0	
				30.0				✓	48.0	
				100.0				✓	160.0	
1415	228769	BG66403	po	30.0				✓	48.0	
				100.0				✓	160.0	
1416	228710	BG66412	sc	10.0	✓				23.0	\sim LD ₅₀
				30.0					69.0	$>$ LD ₁₀₀
				100.0					230.0	$>$ LD ₁₀₀
1416	228710	BG66412	po	30.0					69.0	$>$ LD ₁₀₀
				100.0					230.0	$>$ LD ₁₀₀

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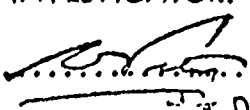
TABLE 28

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1417	228708	BG66798	sc	10.0	✓				21.0	
				30.0	✓				63.0	
				100.0	✓				210.0	\sim LD ₆₆
1417	228708	BG66798	po	30.0	✓				63.0	
				100.0					210.0	> LD ₁₀₀
1418	229046	BG67179	sc	30.0		✓			78.0	
				100.0	✓				260.0	
1418	229046	BG67179	po	30.0				✓	78.0	
				100.0				✓	260.0	
1419	229011	BG67099	sc	30.0		✓			60.0	
				100.0	✓				200.0	\sim LD ₅₀
1419	229011	BG67099	po	30.0				✓	60.0	
				100.0			✓		200.0	
1420	229092	BG68354	sc	30.0				✓	87.0	
				100.0				✓	290.0	
1420	229092	BG68354	po	30.0				✓	87.0	
				100.0				✓	290.0	

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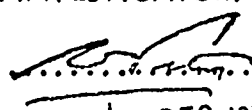

TABLE 29

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1421	229238	BG70112	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1421	229238	BG70112	po	30.0				✓	60.0	
				100.0			✓		200.0	
1422	194965	BG33940	sc	30.0	✓				81.0	
				60.0	✓				162.0	
1422	194965	BG33940	po	30.0				✓	81.0	
				100.0		✓			270.0	
1423	225449	ZN43971	sc	30.0	✓				84.0	
				100.0	✓				280.0	
1423	225449	ZN43971	po	30.0	✓				84.0	
				100.0	✓				280.0	
1426	226292	BG44541	sc	30.0					69.0	> LD ₁₀₀
				100.0					230.0	> LD ₁₀₀
1427	211666	BG11417	sc	30.0	✓				72.0	
				100.0	✓				240.0	
1428	212579	BG48969	sc	30.0				✓	63.0	
				100.0	✓				210.0	

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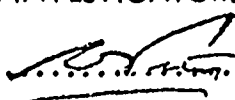
TABLE 30

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1429	226257	BG44425	sc	30.0	✓				60.0	
				100.0	✓				200.0	
1430	129577	AW41662	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1430	129577	AW41662	po	30.0				✓	60.0	
				100.0				✓	200.0	
1431	6026	AG75499	sc	30.0				✓	72.0	
				100.0	✓				240.0	~ LD ₆₆
1431	6026	AG75499	po	30.0	✓				72.0	
				100.0	✓				240.0	
1432	106147	AY97897	sc	30.0				✓	66.0	
				100.0	✓				220.0	
1432	106147	AY97897	po	30.0	✓				66.0	
				100.0	✓				220.0	~ LD ₃₃
1433	202437	BD26164	sc	30.0	✓				51.0	
				100.0	✓				170.0	
1433	202437	BD26164	po	30.0	✓				51.0	
				100.0	✓				170.0	

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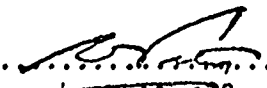
TABLE 31

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1434	203607	BD27652	sc	30.0				✓	42.0	
				100.0	✓				140.0	
1434	203607	BD27652	po	30.0	✓				42.0	
				100.0	✓				140.0	
1435	205439	BD54195	sc	30.0				✓	54.0	
				100.0	✓				180.0	
1435	205439	BD54195	po	3.0			✓		5.4	
				10.0	✓				18.0	
				30.0	✓				54.0	
1436	211533	BE12601	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1436	211533	BE12601	po	30.0			✓		60.0	
				100.0					200.0	> LD ₁₀₀
1437	218335	BE66930	po	30.0	✓				63.0	
				100.0	✓				210.0	~ LD ₅₀

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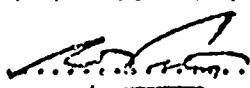
TABLE 32

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	uM Base/Kg	Comment
1438	225448	BG37402	sc	30.0	✓				57.0	~LD ₆₆
				100.0					190.0	>LD ₁₀₀
1438	225448	BG37402	po	30.0	✓				57.0	
				100.0	✓				190.0	~LD ₆₆
1439	221527	BG48898	sc	3.0	✓				7.5	
				10.0					25.0	>LD ₁₀₀
				30.0					75.0	>LD ₁₀₀
				100.0					250.0	>LD ₁₀₀
1439	221527	BG48898	po	30.0					75.0	>LD ₁₀₀
				100.0					250.0	>LD ₁₀₀
1440	229431	BG70578	sc	30.0				✓	60.0	
				60.0			✓		120.0	
1440	229431	BG70578	po	30.0				✓	60.0	
				100.0				✓	200.0	
1441	229397	BG70596	sc	30.0			✓		57.0	
				60.0			✓		114.0	
1441	229397	BG70596	po	30.0				✓	57.0	
				100.0			✓		190.0	

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TABLE 33

Category 1 = ? Fully active = 0/3 Patent

2 = ? Active = 1/3 Patent

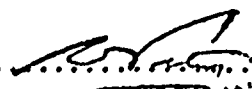
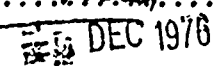
3 = ? Slightly active = 2/3 Patent

4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	µM Base/Kg	Comment
1442	229406	BG70603	sc	30.0				✓	57.0	
				60.0				✓	114.0	
1442	229406	BG70603	po	30.0				✓	57.0	
				100.0				✓	190.0	
1443	229396	BG70630	sc	30.0				✓	57.0	
				60.0			✓		114.0	
1443	229396	BG70630	po	30.0				✓	57.0	
				100.0				✓	190.0	
1444	229398	BG70658	sc	30.0				✓	57.0	
				60.0				✓	114.0	
1444	229398	BG70658	po	30.0				✓	57.0	
				100.0				✓	190.0	
1445	228583	BG70729	sc	30.0					69.0	> LD ₁₀₀
				60.0					138.0	> LD ₁₀₀
1445	228583	BG70729	po	30.0	✓				69.0	
				100.0					230.0	> LD ₁₀₀

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed Date 

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

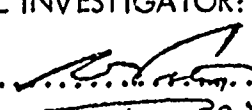
TABLE 34

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1446	228708	BG70756	sc	30.0	✓				63.0	
				60.0	✓				126.0	
1446	228708	BG70756	po	30.0		✓			63.0	
				100.0					210.0	> LD ₁₀₀
1447	201678	ZN40130	sc	30.0			✓		66.0	
				100.0	✓				220.0	
1447	201678	ZN40130	po	30.0	✓				66.0	
				100.0	✓				220.0	
1448	211532	ZN41048	sc	30.0				✓	57.0	
				100.0				✓	190.0	
1448	211532	ZN41048	po	30.0				✓	57.0	
				100.0				✓	190.0	
1449	203608	ZN42125	sc	30.0				✓	42.0	
				100.0		✓			140.0	
1449	203608	ZN42125	po	30.0		✓			42.0	
				100.0	✓				140.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed ... 

Date ... DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

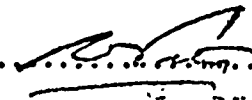
TABLE 35

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	uM Base/Kg	Comment
1450	215296	ZN42812	sc	30.0	✓				66.0	
				100.0	✓				220.0	
1450	215296	ZN42812	po	30.0	✓				66.0	
				100.0	✓				220.0	
1451	219874	ZN42821	sc	30.0				✓	75.0	
				100.0		✓			250.0	
1451	219874	ZN42821	po	30.0					75.0	> LD ₁₀₀
				100.0					250.0	> LD ₁₀₀
1452	215733	ZN43328	sc	30.0				✓	75.0	
				100.0			✓		250.0	~ LD ₃₃
1452	215733	ZN43328	po	30.0				✓	75.0	
				100.0					250.0	> LD ₁₀₀
1453	212223	ZN43391	sc	30.0				✓	72.0	
				100.0	✓				240.0	
1453	212223	ZN43391	po	30.0		✓			72.0	
				100.0	✓				240.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed ... 

Date ... 15 DEC 1970

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

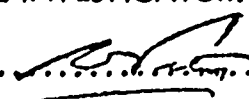
TABLE 36

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x l	1	2	3	4	μ M Base/Kg	Comment
1454	216804	ZN43426	sc	30.0	✓				60.0	
				100.0	✓				200.0	
1454	216804	ZN43426	po	30.0					60.0	> LD ₁₀₀
				100.0					200.0	> LD ₁₀₀
1455	215761	ZN44030	sc	30.0	✓				60.0	
				100.0	✓				200.0	
1455	215761	ZN44030	po	30.0	✓				60.0	
				100.0	✓				200.0	
1470	224097	ZN43953	sc	30.0				✓	60.0	
				100.0			✓		200.0	
1470	224097	ZN43953	po	30.0				✓	60.0	
				100.0		✓			200.0	
1471	229429	BG70667	sc	30.0				✓	54.0	
				100.0				✓	180.0	
1471	229429	BG70667	po	30.0				✓	54.0	
				100.0				✓	180.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed ... 

Date DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

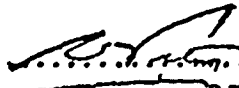
TABLE 37

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x l	1	2	3	4	µM Base/Kg	Comment
1472	229427	BG70550	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1472	229427	BG70550	po	30.0			✓		60.0	
				100.0		✓			200.0	
1473	4396	BG66421	sc	30.0				✓	63.0	
				100.0				✓	210.0	~ LD ₆₆
1473	4396	BG66421	po	30.0				✓	63.0	
				100.0					210.0	> LD ₁₀₀
1474	206513	BG79017	sc	30.0			✓		63.0	
				100.0			✓		210.0	
1474	206513	BG79017	po	30.0			✓		63.0	
				100.0		✓			210.0	
1476	230388	BG81580	po	30.0	✓				72.0	
				100.0					240.0	> LD ₁₀₀
1477	230395	BG81599	po	30.0				✓	54.0	
				100.0				✓	180.0	
1478	230394	BG81606	po	30.0				✓	54.0	
				100.0				✓	180.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed ... 

Date DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

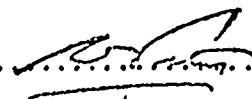
TABLE 38

Category 1 = ? Fully active = 0/3 Patent
 2 = ? Active = 1/3 Patent
 3 = ? Slightly active = 2/3 Patent
 4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μ M Base/Kg	Comment
1479	230387	BG81615	po	30.0				✓	87.0	
				100.0				✓	290.0	
1480	230386	BG81624	po	30.0				✓	66.0	
				100.0			✓		220.0	
1481	230216	BG80967	po	30.0				✓	51.0	
				100.0				✓	170.0	
1482	230212	BG80994	po	30.0				✓	66.0	
				100.0				✓	220.0	
1483	230225	BG81035	po	30.0				✓	63.0	
				100.0				✓	210.0	~ LD ₃₃
1484	230284	BG81222	po	30.0				✓	69.0	
				100.0				✓	230.0	
1485	206287	BG81759	po	30.0				✓	69.0	
				100.0				✓	230.0	
1486	230621	BG83191	po	30.0				✓	69.0	
				100.0			✓		230.0	~ LD ₃₃

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed 

Date DEC 1976

CAUSAL PROPHYLAXIS TEST NO.: BR 531

DATE: 26.11.76

DRUG: LIV/1411

WR 225374

BOTTLE NO. BG

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME AF

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylax activity
0	5/5	3/3	3/3	5.93	3.72	3.71			
3.0	2/3		3/3	>8.59		3.68	> 2.66 - $\left[\frac{1.72 \times 1.68}{1.71} - 1.72 \right]$	-0.03	> 2.69
10.0	3/3*		0/3**	5.72		-	-0.21		
30.0	0/3**		0/3**	-		-			

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY: Nil at 3.0 mg/kg

PRINCIPAL INVE

* 1/3 died ** 3/3 died

2

ST NO.: BR 531 DATE: 26.11.76 TABLE 39

LIV/1411 WR 225374 BOTTLE NO. BG37591

H₂O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.93	3.72	3.71				
> 8.59		3.68	$> 2.66 \left[\frac{1.72 \times 1.68}{1.71} - 1.72 \right]$	-0.03	> 2.69	Slightly active
5.72		-	-0.21			~ LD ₆₆
-		-				> LD ₁₀₀

DOSE.....mg/kg

Nil at 3.0 mg/kg

* 1/3 died ** 3/3 died

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR531

DATE: 26.11.76

DRUG:

LIV/1404

WR 228335

BOTTLE NO. BG

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 25 P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophyl activity
∅	5/5	3/3	3/3	5.93	3.72	3.71			
3.0	2/3		3/3	>8.51		3.71	> 2.58 - $\left[\frac{1.72 \times 1.71}{1.71} - 1.72 \right]$	0	> 2.58
10.0	2/3		3/3	>8.86		4.28	> 2.93 - $\left[\frac{1.72 \times 2.28}{1.71} - 1.72 \right]$	0.57	> 2.36
30.0	0/3		3/3	>14		3.74	> 8.07 - $\left[\frac{1.72 \times 1.74}{1.71} - 1.72 \right]$	0.03	> 8.04

MINIMUM FULLY ACTIVE DOSE.....10.0-30.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 30.0 mg/kg

PRINCIPAL INVE

2

TEST NO.: BR531

DATE: 26.11.76

TABLE 40

LIV/1404

WR 228335

BOTTLE NO. BG 60689

B₀/H₂O

ROUTE OF ADMINISTRATION: ~~ip~~/sc/po TIME AFTER INFECTION: 2 hrs.

FW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P				(a = 2) ACTIVITY VALUES			COMMENT
x	f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
	5.93	3.72	3.71				
>8.51			3.71	$> 2.58 - \left[\frac{1.72 \times 1.71}{1.71} - 1.72 \right]$	0	> 2.58	Slightly active
>8.86			4.28	$> 2.93 - \left[\frac{1.72 \times 2.28}{1.71} - 1.72 \right]$	0.57	> 2.36	Slightly active
>14			3.74	$> 8.07 - \left[\frac{1.72 \times 1.74}{1.71} - 1.72 \right]$	0.03	> 8.04	Fully active

VE DOSE.....10.0-30.0.....mg/kg

Nil at 30.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 531

DATE: 26.11.76

DRUG:

LIV/1403

WR 228327

BOTTLE NO. BG

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylac activity
Ø	5/5	3/3	3/3	5.93	3.72	3.71			
60.0	1/3		3/3	>11.27		3.77	> 5.34 - $\left[\frac{1.72 \times 1.77}{1.71} - 1.72 \right]$	0.06	> 5.2
100.0	0/3		3/3	>14		3.74	> 8.07 - $\left[\frac{1.72 \times 1.74}{1.71} - 1.72 \right]$	0.03	> 8.0

MINIMUM FULLY ACTIVE DOSE.....⁶⁰⁻¹⁰⁰mg/kg

RESIDUAL ACTIVITY: Nil at 100.0 mg/kg

PRINCIPAL INVESTIGATOR

NO.: BR 531

DATE: 26.11.76

TABLE 41

LIV/1403

WR 228327

BOTTLE NO. BG60698

H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.93	3.72	3.71				
> 11.27		3.77	$> 5.34 - \left[\frac{1.72 \times 1.77}{1.71} - 1.72 \right]$	0.06	> 5.28	Active
> 14		3.74	$> 8.07 - \left[\frac{1.72 \times 1.74}{1.71} - 1.72 \right]$	0.03	> 8.04	Fully active

DOSE.....60-100 mg/kg

Nil at 100.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 563

DATE: 17.1.77

DRUG: LIV/1402

WR 228002

BOTTLE NO. B

PREPARATION: Tween 80/H₂OROUTE OF ADMINISTRATION: ~~ip~~/sc/po TIME A

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylax activity
∅	5/5	3/3	3/3	5.35	4.95	3.63			
3.0	0/3		3/3	>14.00		4.05	$> 8.65 - \left[\frac{2.95 \times 2.05}{1.63} - 2.95 \right]$	0.76	> 7.8
10.0	0/3		3/3	>14.00		3.91	$> 8.65 - \left[\frac{2.95 \times 1.91}{1.63} - 2.95 \right]$	0.51	> 8.1
30.0	0/3*		0/3**	>14.00		-			

MINIMUM FULLY ACTIVE DOSE.....<3.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 10.0 mg/kg

PRINCIPAL INVE

* 2/3 died 1** 3/3 died

2

NO.: BR 563

DATE: 17.1.77

TABLE 42

LIV/1402

WR 228002

BOTTLE NO. BG 58189

H₂O

ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.35	4.95	3.63				.
>14.00		4.05	$> 8.65 - \left[\frac{2.95 \times 2.05}{1.63} - 2.95 \right]$	0.76	> 7.89	Fully active
>14.00		3.91	$> 8.65 - \left[\frac{2.95 \times 1.91}{1.63} - 2.95 \right]$	0.51	> 8.14	Fully active
>14.00		-				$\sim LD_{80}$

DOSE..... ≤ 3.0mg/kg

at 10.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

3/3 died 1** 3/3 died

CAUSAL PROPHYLAXIS TEST NO.: BR 563

DATE: 17.1.77

DRUG:

LIV/1401

WR 227988

BOTTLE NO. BG 58

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER

VERTEBRATE HOST: ♂TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylact activity
Ø	5/5	3/3	3/3	5.35	4.95	3.63			
100.0	3/3		3/3	5.11		3.40	-0.24 - $\left[\frac{2.95 \times 1.40}{1.63} - 2.95 \right]$	-0.41	0.17
300.0	3/3		3/3	5.35		3.72	0 - $\left[\frac{2.95 \times 1.72}{1.63} - 2.95 \right]$	0.16	-0.16

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY:

Nil at 300.0 mg/kg

PRINCIPAL INVEST

2

NO.: BR 563

DATE: 17.1.77

TABLE 43

LIV/1401

WR 227988

BOTTLE NO. BG 58447

H₂O
mice

ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.35	4.95	3.63				
5.11		3.40	$-0.24 - \left[\frac{2.95 \times 1.40}{1.63} - 2.95 \right]$	-0.41	0.17	Inactive
5.35		3.72	$0 - \left[\frac{2.95 \times 1.72}{1.63} - 2.95 \right]$	0.16	-0.16	Inactive

DOSE.....mg/kg

Nil at 300.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 563

DATE: 17.1.77

DRUG:

LIV/ 1400

WR 228000

BOTTLE NO.

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C^0/T^0	XC	C^x/T^x	f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophyl activit
∅	5/5	3/3	3/3	5.35	4.95	3.63			
60.0	0/3*		1/3**	-		4.18			

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INV

*3/3 died ** 2/3 died

2

ST NO.: BR 563

DATE: 17.1.77

TABLE 4:

LIV/ 1400

WR 228000

BOTTLE NO. BG58367

D/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

W mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES		Residual activity	Prophylactic activity	COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$				
5.35	4.95	3.63					
-		4.18					~LD ₈₀

E DOSE.....mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

ed ** 2/3 died

CAUSAL PROPHYLAXIS TEST NO.: BR564

DATE: 20.1.77

DRUG: LIV/1399

WR 227681

BOTTLE NO.

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophyl activity
∅	5/5	3/3	2/2	5.30	3.67	4.05			
60.0	1/3		3/3	>11.17		3.85	> 5.87 - $\left[\frac{1.67 \times 1.85}{2.05} - 1.67 \right]$	-0.16	> 6.
100.0	0/3		0/3	>14.00		>14.00	> 8.70 - $\left[\frac{1.67 \times 12.00}{2.05} - 1.67 \right]$	8.11	> 0.

MINIMUM FULLY ACTIVE DOSE.....60-100.....mg/kg

RESIDUAL ACTIVITY: Very marked at 100 mg/kg

PRINCIPAL INVESTIGATOR

2

NO.: BR564

DATE: 20.1.77

TABLE 45

LIV/1399

WR 227681

BOTTLE NO. BG 56612

ROUTE OF ADMINISTRATION: ~~ip/sc/po~~ TIME AFTER INFECTION: 2 hrs.

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

20
mice

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/a	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.30	3.67	4.05				
11.17		3.85	$> 5.87 - \left[\frac{1.67 \times 1.85}{2.05} - 1.67 \right]$	-0.16	> 6.03	Active
14.00		> 14.00	$> 8.70 - \left[\frac{1.67 \times 12.00}{2.05} - 1.67 \right]$	8.11	> 0.59	Prophylactic activity masked by strong residual activity

DOSE.....60-100.....mg/kg

marked at 100 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 564

DATE: 20.1.77

DRUG:

LIV/1395

WR 199361

BOTTLE NO. B

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophyla activity
∅	5/5	3/3	2/2	5.30	3.67	4.05			
1.0	3/3		3/3	6.35		3.95	$1.05 - \left[\frac{1.67 \times 1.95}{2.05} - 1.67 \right]$	-0.08	1
3.0	0/6		3/3	>14.00		4.78	$> 8.70 - \left[\frac{1.67 \times 2.78}{2.05} - 1.67 \right]$	0.59	> 8
10.0	0/3		3/3	>14.00		5.61	$> 8.70 - \left[\frac{1.67 \times 3.61}{2.05} - 1.67 \right]$	1.27	> 7

MINIMUM FULLY ACTIVE DOSE.....1.0-3.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 3.0 mg/kg
Slight at 10.0 mg/kg

PRINCIPAL INVE

2

TEST NO.: BR 564

DATE: 20.1.77

TABLE 46

LIV/1395

WR 199361

BOTTLE NO. BG 47168

H₂O

ROUTE OF ADMINISTRATION: ~~ip~~/sc/po TIME AFTER INFECTION: 2 hrs.

FW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

x	GMP 2% P			(a = 2) ACTIVITY VALUES		COMMENT
	f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity
2	5.30	3.67	4.05			
3	6.35		3.95	$1.05 - \left[\frac{1.67 \times 1.95}{2.05} - 1.67 \right]$	-0.08	1.13
3	>14.00		4.78	$> 8.70 - \left[\frac{1.67 \times 2.78}{2.05} - 1.67 \right]$	0.59	> 8.11
3	>14.00		5.61	$> 8.70 - \left[\frac{1.67 \times 3.61}{2.05} - 1.67 \right]$	1.27	> 7.43

VE DOSE.....1.0-3.0.....mg/kg

Nil at 3.0 mg/kg
Slight at 10.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 536

DATE: 6.12.76

DRUG:

LIV/1394

WR 226626

BOTTLE NO. BG4

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME AF

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylax activity
∅	5/5	3/3	3/3	5.10	5.02	3.59			
1.0	2/3		3/3	> 8.10		3.53	> 3.00 - $\left[\frac{3.02 \times 1.53}{1.59} - 3.02 \right]$	-0.11	> 3.11
3.0	0/3		3/3	> 14		3.45	> 8.90 - $\left[\frac{3.02 \times 1.45}{1.59} - 3.02 \right]$	-0.27	> 9.17
10.0	0/3		2/2	> 14		3.68	> 8.90 - $\left[\frac{3.02 \times 1.68}{1.59} - 3.02 \right]$	0.17	> 8.73

MINIMUM FULLY ACTIVE DOSE.....1.0-3.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 10.0 mg/kg

PRINCIPAL INVEST

2

NO.: BR 536

DATE: 6.12.76

TABLE 47

LIV/1394

WR 226626

BOTTLE NO. BG46714

H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.10	5.02	3.59				
> 8.10		3.53	$> 3.00 - \left[\frac{3.02 \times 1.53}{1.59} - 3.02 \right]$	-0.11	> 5.11	Slightly active
> 14		3.45	$> 8.90 - \left[\frac{3.02 \times 1.45}{1.59} - 3.02 \right]$	-0.27	> 9.17	Fully active
> 14		3.68	$> 8.90 - \left[\frac{3.02 \times 1.68}{1.59} - 3.02 \right]$	0.17	> 8.72	Fully active

DOSE.....1.0-3.0.....mg/kg

Nil at 10.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 532

DATE: 30.11.76

DRUG:

LIV/ 1393

WR 226426

BOTTLE NO. B

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o / _T ^o	XC	C ^x / _T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophyl activity
∅	5/5	3/3	3/3	5.26	3.67	3.66			
0.3	2/3		3/3	> 8.71		4.01	> 3.45 - $\left[\frac{1.67 \times 2.01}{1.66} - 1.67 \right]$	0.35	> 3.1
1.0	1/3		3/3	> 11.60		4.15	> 6.34 - $\left[\frac{1.67 \times 2.15}{1.66} - 1.67 \right]$	0.49	> 5.8
3.0	0/3		3/3	> 14		3.92	> 8.74 - $\left[\frac{1.67 \times 1.92}{1.66} - 1.67 \right]$	0.26	> 8.4

MINIMUM FULLY ACTIVE DOSE.....1.0 - 3.0 mg/kg

RESIDUAL ACTIVITY: Nil at 3.0 mg/kg

PRINCIPAL INVE

2

TEST NO.: BR 532

DATE: 30.11.76

TABLE 48

LIV/ 1393

WR 226426

BOTTLE NO. BG 45208

90/H₂OROUTE OF ADMINISTRATION: ~~ip~~/sc/po TIME AFTER INFECTION: 2 hrs.

FEW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

x	GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
3	5.26	3.67	3.66				
3	> 8.71		4.01	$> 3.45 - \left[\frac{1.67 \times 2.01}{1.66} - 1.67 \right]$	0.35	> 3.10	Slightly active
3	> 11.60		4.15	$> 6.34 - \left[\frac{1.67 \times 2.15}{1.66} - 1.67 \right]$	0.49	> 5.85	Active
3	> 14		3.92	$> 8.74 - \left[\frac{1.67 \times 1.92}{1.66} - 1.67 \right]$	0.26	> 8.48	Fully active

VE DOSE.....1.0 - 3.0 m.....mg/kg

Nil at 3.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 536

DATE: 6.12.76

DRUG:

LIV/1392

WR 215761

BOTTLE NO. BE 1

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylax activity
∅	5/5	3/3	3/3	5.10	5.02	3.59			
30.0	0/3		3/3	>14		3.52	$> 8.90 - \left[\frac{3.02 \times 1.52}{1.59} - 3.02 \right]$	-0.13	>9.2

MINIMUM FULLY ACTIVE DOSE.....^{<30}.....mg/kg

RESIDUAL ACTIVITY: Nil at 30.0 mg/kg

PRINCIPAL INVESTIGATOR

2

T. NO.: BR 536

DATE: 6.12.76

TABLE 49

LIV/ 1392

WR 215761

BOTTLE NO. BE 16967

H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.10	5.02	3.59				
> 14		3.52	$> 8.90 - \left[\frac{3.02 \times 1.52}{1.59} - 3.02 \right]$	-0.13	> 9.20	Fullv active

DOSE.....<30.....mg/kg

Nil at 30.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 536

DATE: 6.12.76

DRUG:

LIV/1391

WR 226296

BOTTLE NO. B

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME

VERTEBRATE HOST: ♂TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophy activi
∅	5/5	3/3	3/3	5.10	5.02	3.59			
0.3	3/3		3/3	5.01		3.83	$-0.09 - \left[\frac{3.02 \times 1.83}{1.59} - 3.02 \right]$	0.46	-0
1.0	2/3		3/3	> 8.47		4.51	$> 3.37 - \left[\frac{3.02 \times 2.51}{1.59} - 3.02 \right]$	1.75	> 1

MINIMUM FULLY ACTIVE DOSE.....>1.0.....mg/kg

RESIDUAL ACTIVITY: Slight at 1.0 mg/kg

PRINCIPAL INV

2

NO.: BR 536

DATE: 6.12.76

TABLE 50

LIV/1391

WR 226296

BOTTLE NO. BG44452

H₂O

ROUTE OF ADMINISTRATION: ~~ip/sc/po~~ TIME AFTER INFECTION: 2 hrs.

W. mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.10	5.02	3.59				
5.01		3.83	$-0.09 - \left[\frac{3.02 \times 1.83}{1.59} - 3.02 \right]$	0.46	-0.55	Inactive
> 8.47		4.51	$> 3.37 - \left[\frac{3.02 \times 2.51}{1.59} - 3.02 \right]$	1.75	> 1.62	Slightly active

DOSE.....> 1.0.....mg/kg

Slight at 1.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 536

DATE: 6.12.76

DRUG:

LIV/1390

WR 211533

BOTTLE NO. BG

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophyl activity
∅	5/5	3/3	3/3	5.10	5.02	3.59			
100.0	3/3		3/3	5.39		3.75	0.29 - $\left[\frac{3.02 \times 1.75}{1.59} - 3.02 \right]$	0.30	-0.0
150.0	3/3		2/3*	5.90		3.54	0.80 - $\left[\frac{3.02 \times 1.54}{1.59} - 3.02 \right]$	-0.10	0.9

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY: Nil at 150.0 mg/kg

PRINCIPAL INVE

* 1/3 died

2

EST NO.: BR 536

DATE: 6.12.76

TABLE 51

LIV/1390

WR 211533

BOTTLE NO. BG 38034

H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

FW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P				(a = 2) ACTIVITY VALUES			COMMENT
x	f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
3	5.10	5.02	3.59				
3	5.39		3.75	$0.29 - \left[\frac{3.02 \times 1.75}{1.59} - 3.02 \right]$	0.30	-0.01	Inactive
3*	5.90		3.54	$0.80 - \left[\frac{3.02 \times 1.54}{1.59} - 3.02 \right]$	-0.10	0.90	Inactive

VE DOSE.....mg/kg

Nil at 150.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

1/3 died

CAUSAL PROPHYLAXIS TEST NO.: BR532

DATE: 30.11.76

DRUG: LIV/1387

WR 219874

BOTTLE NO. BE

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂ TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C ^o /T ^o	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophyl activity
∅	5/5	3/3	3/3	5.26	3.67	3.66			
1.0	1/3		3/3	>11.30		4.33	> 6.04 - $\left[\frac{1.67 \times 2.33}{1.66} - 1.67 \right]$	0.67	> 5.3
3.0	0/3		3/3	>14		4.66	> 8.74 - $\left[\frac{1.67 \times 2.66}{1.66} - 1.67 \right]$	1.01	> 7.7

MINIMUM FULLY ACTIVE DOSE..... 1.0 - 3.0 mg/kg

RESIDUAL ACTIVITY: Slight at 3.0 mg/kg

PRINCIPAL INVE

21

IT NO.: BR532

DATE: 30.11.76

TABLE 52

LIV/1387

WR 219874

BOTTLE NO. BE 79802

H₂O

ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.26	3.67	3.66				
>11.30		4.33	$> 6.04 - \left[\frac{1.67 \times 2.33}{1.66} - 1.67 \right]$	0.67	> 5.37	Active
>14		4.66	$> 8.74 - \left[\frac{1.67 \times 2.66}{1.66} - 1.67 \right]$	1.01	> 7.73	Fully active

DOSE..... 1.0 - 3.0mg/kg

Slight at 3.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR532

DATE: 30.11.76

DRUG:

LIV/1386

WR 217154

BOTTLE NO. BE

PRÉPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: ip/sc/po TIME

VÉRTEBRATE HOST: ♂TFW mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	C°/T°	XC	C ^x /T ^x	f/h	b	c/e	(h - f) - $\left[\frac{(b - a)(e - a)}{(c - a)} - (b - a)\right]$	Residual activity	Prophyl activity
∅	5/5	3/3	3/3	5.26	3.67	3.66			
30.0	2/3		3/3	> 8.66		3.60	> 3.40 - $\left[\frac{1.67 \times 1.60}{1.66} - 1.67\right]$	-0.06	> 3.
60.0	1/3		3/3	>11.46		3.55	> 6.20 - $\left[\frac{1.67 \times 1.55}{1.66} - 1.67\right]$	-0.11	> 6.

MINIMUM FULLY ACTIVE DOSE.....>60.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 60.0 mg/kg

PRINCIPAL INVE

2

ST NO.: BR532

DATE: 30.11.76

TABLE 53

LIV/1386

WR 217154

BOTTLE NO. BE 67204

H₂OROUTE OF ADMINISTRATION: ~~ip/sc/po~~ TIME AFTER INFECTION: 2 hrs.

W. mice

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
f/h	b	c/e	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a) \right]$	Residual activity	Prophylactic activity	
5.26	3.67	3.66				
> 8.66		3.60	$> 3.40 - \left[\frac{1.67 \times 1.60}{1.66} - 1.67 \right]$	-0.06	> 3.34	Slightly active
> 11.46		3.55	$> 6.20 - \left[\frac{1.67 \times 1.55}{1.66} - 1.67 \right]$	-0.11	> 6.09	Active

E DOSE.....>60.0.....mg/kg

Nil at 60.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

TABLE 54

The relationship between parasitaemia and catheptic activity
in P. berghēi-infected mouse erythrocytes

Experiment	Day	Parasitaemia (%)	Catheptic activity per cell*	
			All cells	Parasitized cells
I	4	10	1.98	19.8
	5	18	1.22	6.8
	6	29	1.73	5.9
	7	39	1.43	3.7
II	3	5	2.55	51.0
	5	14	2.85	20.4
	6	30	4.43	14.54
	.	38	2.61	6.77
	10	42	6.13	2.62

* arbitrary units

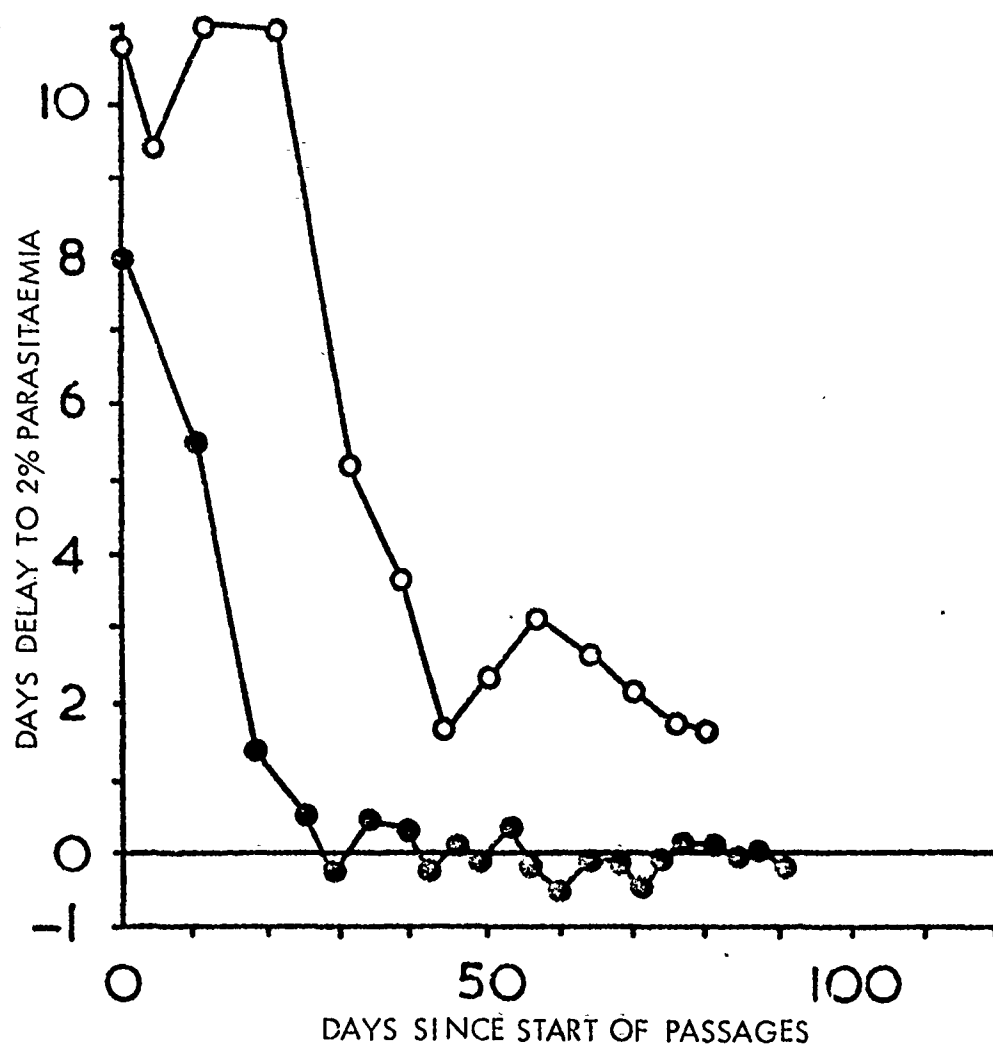


FIGURE 1

A comparison of the rate of acquisition of resistance to mefloquine by the chloroquine-sensitive *P. berghei* N strain and the NS line which has a low level of resistance to chloroquine.

○—○ N strain exposed to a single dose of 30 mg/kg mefloquine on the day of passage.

●—● NS line exposed to 60 mg/kg mefloquine sc on the day of passage.

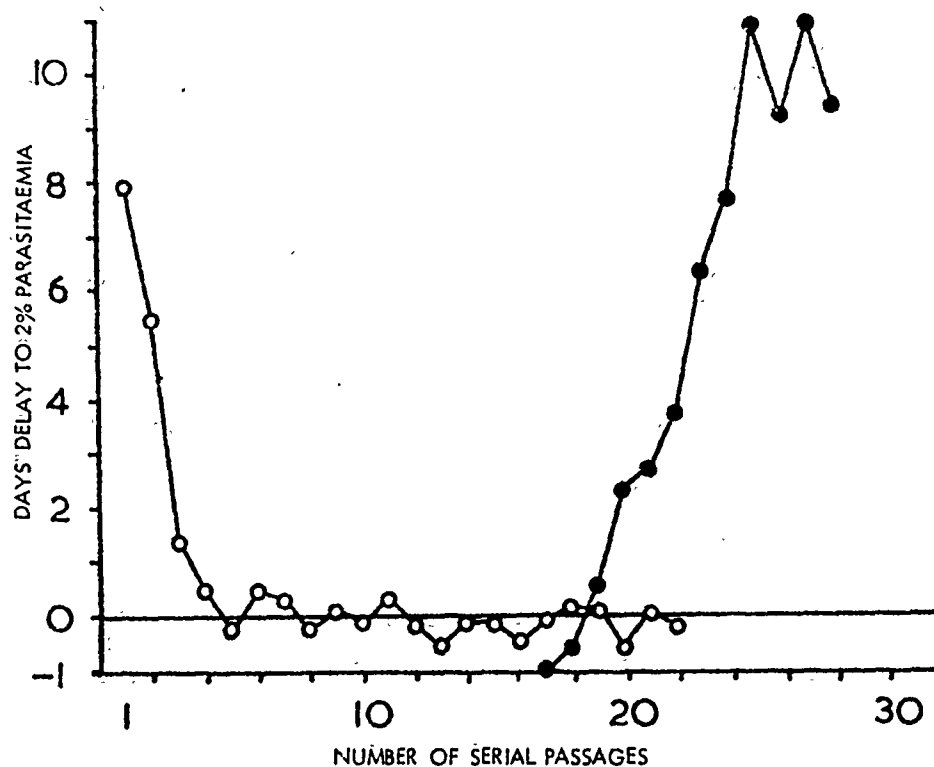


FIGURE 2

The acquisition of resistance to mefloquine by *P. berghei* NS line passaged under drug pressure (mefloquine 60 mg/kg sc at time of each passage), and its reversion to sensitivity on the release of drug selection pressure.

- passages under drug pressure.
- passages without selection pressure.

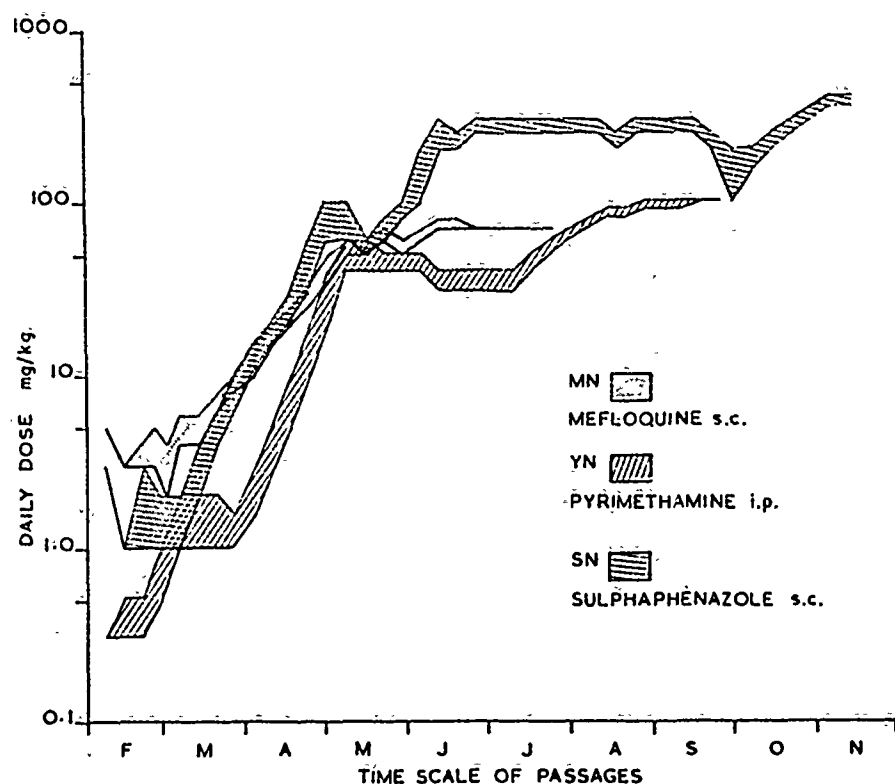


FIGURE 3.

Rate of acquisition by *P. berghei* N strain of resistance to mefloquine, pyrimethamine and sulphaphenazole when the drugs are used alone. Consecutive passages were exposed to increasing drug doses, given daily for 6 days of each week, the passages being made on the 7th day.

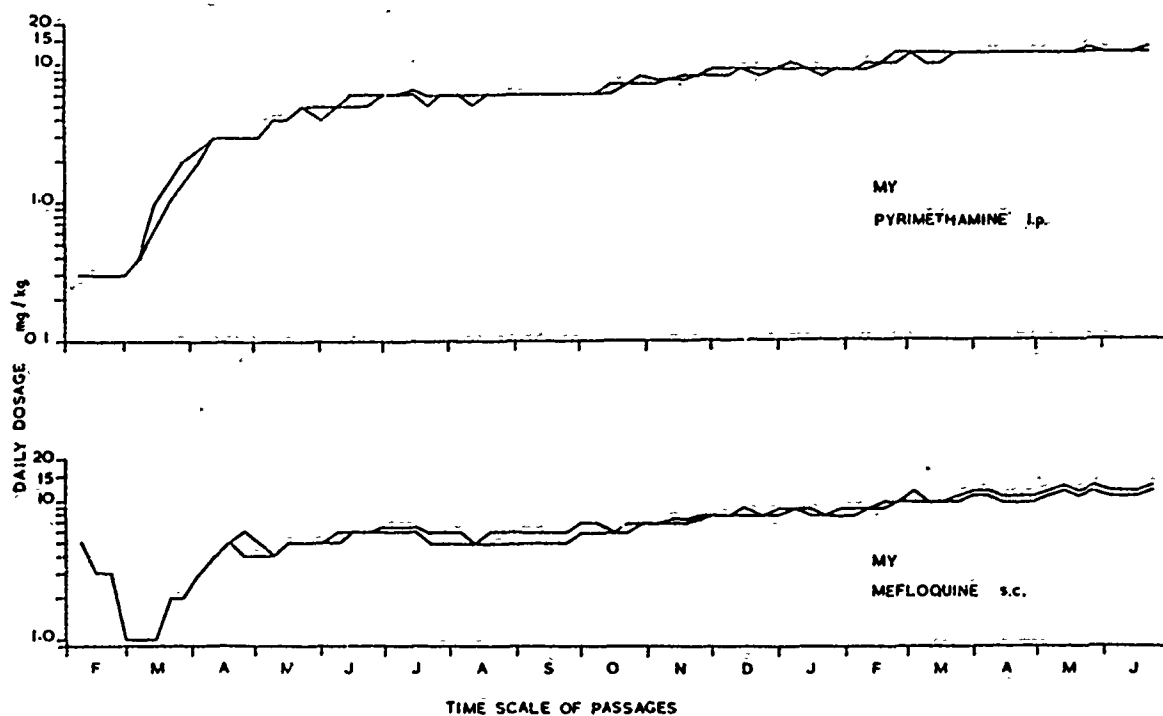


FIGURE 4

Influence of combining mefloquine with pyrimethamine on the rate of acquisition of resistance to each drug by *P. berghei* in consecutive passages. Top lines indicate maximum levels of pyrimethamine and lower lines of mefloquine in the mixture at each passage (cf Figure 3).

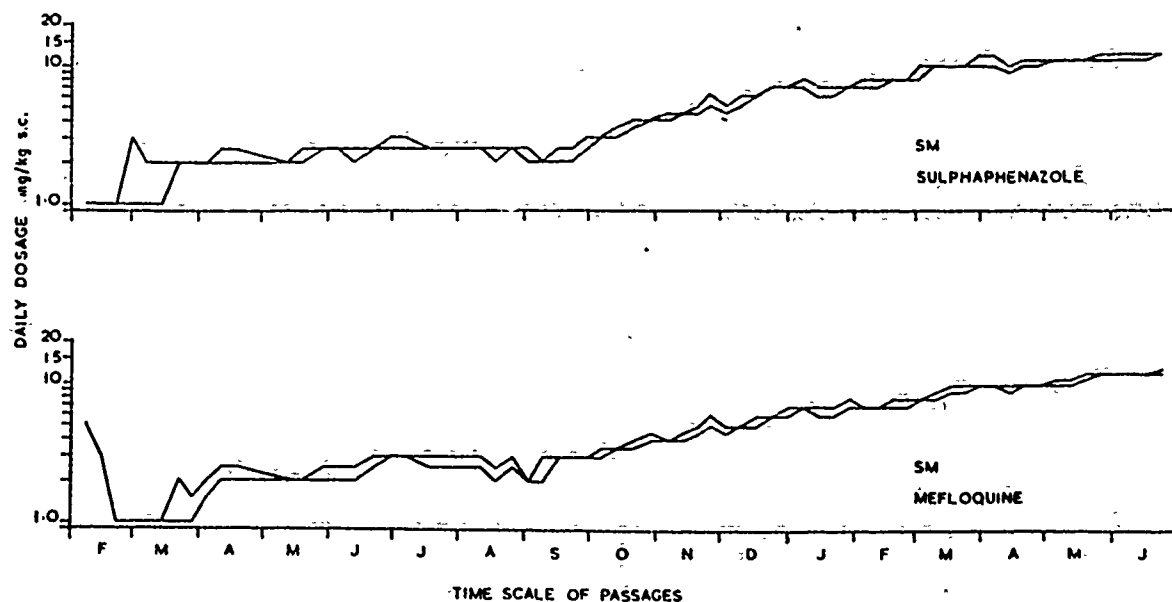


FIGURE 5

Influence of combining mefloquine with sulphaphenazole on the rate of acquisition of resistance to each drug by *P. berghei* N strain in consecutive passages. Top lines indicate maximum levels of sulphaphenazole and bottom lines of mefloquine in the mixtures at each passage (cf Figure 3).

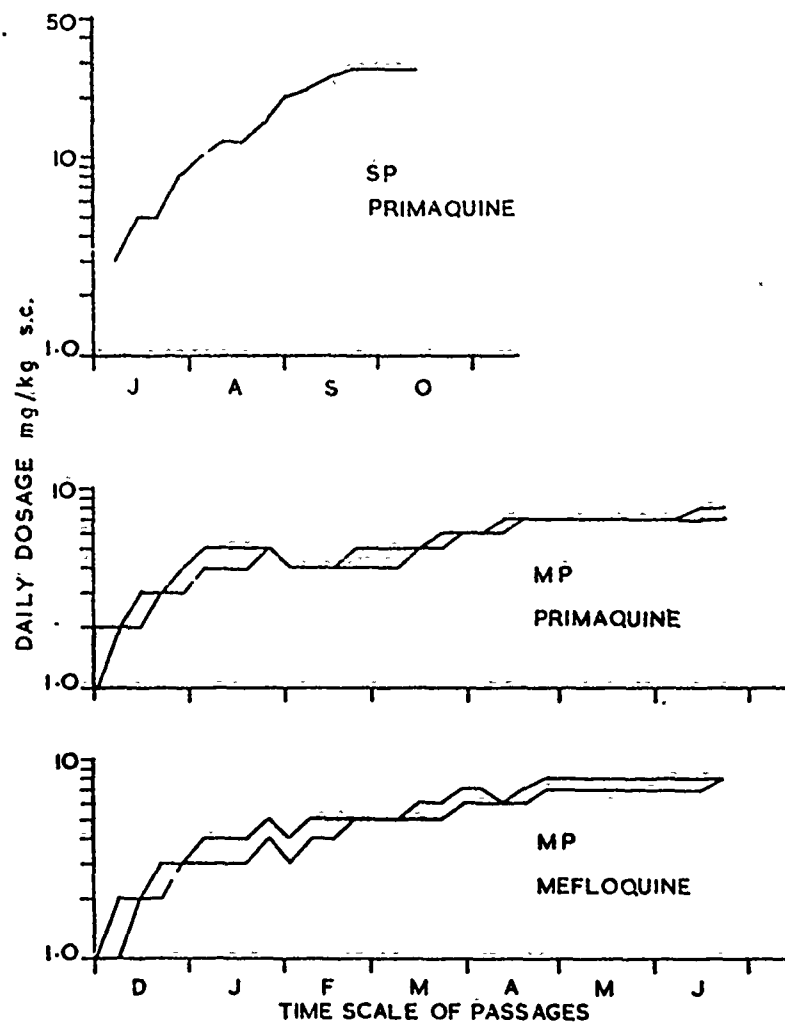


FIGURE 6

Influence of combining mefloquine with primaquine on the rate of acquisition of resistance to each drug by *P. berghei* in consecutive passages. Top lines indicate maximum level of primaquine in SP line exposed to primaquine alone. Middle line indicates maximum levels of primaquine and bottom of mefloquine in the mixtures at each passage.

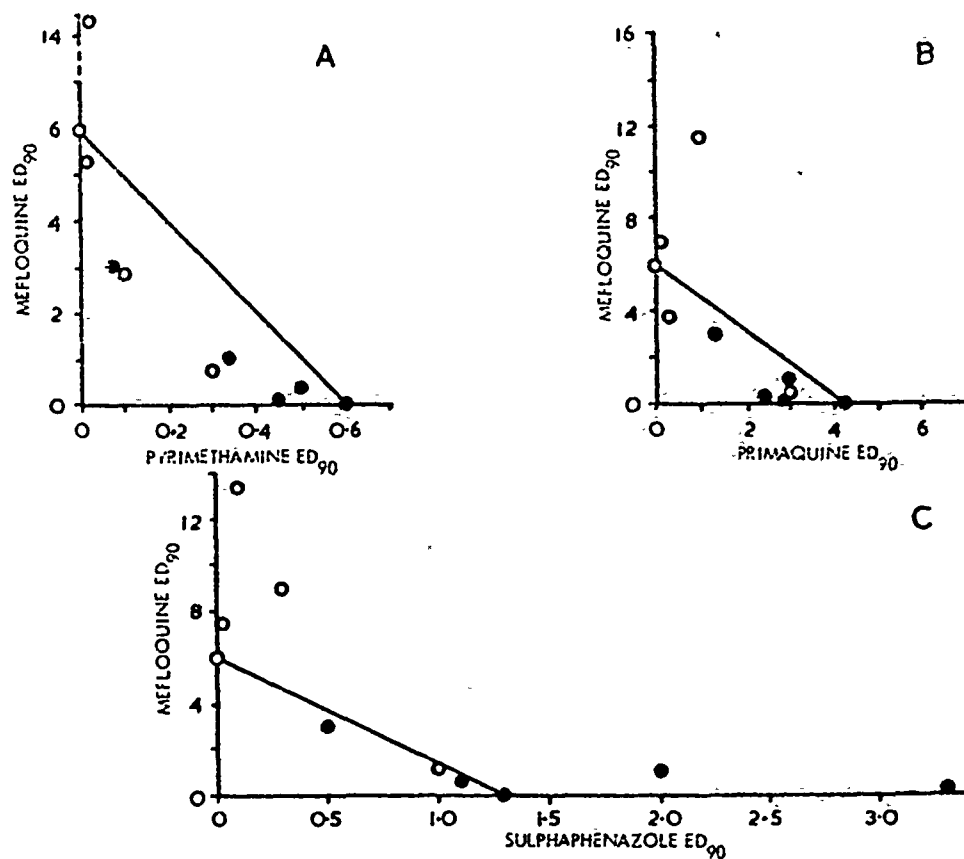


FIGURE 7

Blood schizontocidal action of drug mixtures against *P. berghei* N strain in the "4 day test". The graphs are plotted to show the ED₉₀ values of mefloquine when given alone or with different doses of (A) pyrimethamine, (B) primaquine, or (C) sulphaphenazole (o), or of the latter when given with different doses of mefloquine (●). (All doses in mg/kg daily x 4).

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